PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Aaron G. Filler et al.	Attorney Docket No:	UOFW16938
Serial No:	08/028,795	Group Art Unit:	
Filed:	March 8, 1993	Examiner:	

Title: IMAGE NEUROGRAPHY AND DIFFUSION ANISOTROPY IMAGING

LETTER TRANSMITTING PRIORITY DOCUMENTS

Seattle, Washington 98101

December 28, 1993

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Enclosed is a certified copy of the following applications for which a claim of priority under 35 U.S.C. § 119 has been made:

Country	Serial No.	Filed	Title
U.K.	9301268.0	January 22, 1993	IMAGES, APPARATUS, ALGORITHMS, METHODS, AND TECHNIQUES
U.K.	9216383.1	July 31, 1992	IMAGES, APPARATUS, ALGORITHMS, AND METHODS
U.K.	9210810.9	May 21, 1992	IMAGES APPARATUS AND METHODS
U.K.	9209648.6	May 5, 1992	IMAGE APPARATUS AND METHOD

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U.K.	9207013.5	March 30, 1992	IMAGING APPARATUS AND METHOD
U.K.	9205541.7	March 13, 1992	IMAGING METHOD AND APPARATUS
U.K.	9205058.2	March 9, 1992	TECHNIQUES (N1)

Respectfully submitted,

CHRISTENSEN, O'CONNOR, JOHNSON & KINDNESS

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on December 28, 1993.

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Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: Images, Apparatus, Algorithms, Methods, and Techniques

❷ Applicant's details

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

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2a If you are applying as a corporate body please give:

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Form SI 77 filed 1/12/93. *Please mark correct box*

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3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

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ADP number *(if known)* 060270599001

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5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

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❻ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

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❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77	1		
Claim(s)	5	Description	27
Abstract	1	Drawing(s)	12

8b Which of the following documents also accompanies the application?

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Priority documents *(please state how many)*	
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IMAGES, APPARATUS, ALGORITHMS AND METHODS

The present invention relates to an imaging method and an apparatus for performing same. In particular, it relates to a new method for making a type of image of the living mammalian body such as of a human. The resultant image is hereinafter referred to as a neurogram or image neurogram and which shows the pattern of the peripheral, autonomic or cranial nerve tree so that it stands out in isolation from other structures. Additionally, the method and apparatus can produce an entirely novel kind of brain image, termed a CNS neurogram, in which a selected neural tract of interest can be effectively traced and so made to stand out in isolation from other neural tracts.

Although many techniques have been developed for showing distinctive images of the brain, spinal cord, and spinal roots within the spinal canal, hitherto there has not been a successful method for creating images of the peripheral, autonomic, and cranial nerves as they pass among bones, muscles, lymphatics, tendons, ligaments, intermuscular septa, collections of fatty tissues, air or fluid spaces, veins, arteries, joints, skin, mucous membranes and other tissues or of cancelling the image signal of these various non-neural tissues in order to appear to enhance the nerve in such a way as to permit neurographic images. The peripheral, autonomic, and cranial nerves are relatively small compared to many other bodily tissues, and they often travel in bundles near other structures of comparable size and shape.

Radiologic methods exist for generating tissue specific images of bone, vessels, lymphatics, GI structures, and the tissues of the central nervous system, but there has been no means to generate a clinical image of a nerve as it passes along its course within the human body.

In some imaging techniques, a nerve can be identified with more or less certainty by reference to known norms of relative position of more conspicuous structures such as tendons, vessels, or bone. In neurography, it is the intrinsic biological properties of the nerve itself and their interactions with e.g. magnetic resonance imaging techniques which allows the non-invasive identification of nerves without reference to their anatomic position in an image. This is exceedingly important because of the variability of nerve position from individual to individual. In existing techniques one can only image regions of the body through which a nerve of interest passes, identify non-neural structures then infer the locations of the nerves from standard reference information about human anatomy.

The lack of a suitable method for creating a distinct image of the nerves in a living mammal or human has been a great hindrance to physicians, surgeons, athletic trainers, and pain treatment specialists. Such a neurogram would also be of great advantage to designers of ergonomic furniture & high gravity air or space craft seats, specialized body suits, boots, and various kinds of electronic or electric medical equipment which can be best used when the positions of nerves can be precisely located in advance.

Although many nerves travel along straight and simple courses, there are very complex nerve arrangements such as the brachial plexus, lumbar plexus, or sacral plexus where bundles of nerves collect together, separate, rejoin, intermix, and resegregate in such a way as to create a very intricate three dimensional pattern. A compression or irritation of a small area of nerve within such a plexus (e.g. in the shoulder) can cause pain, numbness, weakness or paralysis at some distant site (e.g. in one finger). Even when a surgeon attempts to expose and examine the brachial plexus for direct inspection, the anatomic complexity can prove overwhelming, rendering surgery in this area to be extremely difficult and dangerous.

Co-pending PCT Patent Application No. PCT EP 91/01780 (WO 92/04916) describes a method which attempts to make nerves stand out in images by the means of administering pharmaceutical agents which give the nerves special imaging properties. These pharmaceuticals are two-part agents which gain entry into and are transported within nerves where the second part of the agent has an imageable property.

If the second part of the molecule has elements with high nuclear density, then it may tend to increase the contrast of the nerve upon X-ray or Computed Tomography (CT) examination.

If the second part has a radioactive (e.g. positron emitting) element, then the nerve may be visible upon Positron Emission Tomography (PET) scanning, or if the second part has a magnetically active component, then the signal of the nerve may be changed upon Magnetic Resonance Imaging (MRI). These agents are injected into muscle and thereby used selectively to alter the imaging characteristics of the nerve supplying that muscle.

The main limitation with these intraneural pharmaceutical agents is that they can generally be used only to image a single nerve or nerve group. The ferrite MRI agents for nerve imaging actually gain their effect by blacking out the nerve in the image. Since nerves are difficult to see in current types of MRI images, the action of these MRI nerve imaging agents can be difficult to interpret.

The present disclosure relates to a new method, which quite remarkably, is capable of generating a three dimensional image of an individual patient's nerves and nerve plexuses. The image can be acquired non-invasively and rapidly by a magnetic resonance scanner. These images are acquired in such a way that some embodiments of the invention are able to make all other structures in the body including bone, fat, skin, muscle, blood, and connective tissues seem to tend to disappear so that only the nerve tree remains to be seen. A plurality of the nerves passing through a given imaged region may be observed simultaneously thus alleviating any ambiguity of nerve identification which might arise were only a single nerve imaged as with some contrast agent techniques.

The invention is based on the discovery of a method of collecting a data set of spatial coordinates which describes the positions of the nerves within any two dimensional cross section of a living mammal or within any three dimensional data acquisition space. There exist a large number of pulse sequences capable of controlling or operating a magnetic resonance imaging apparatus and each of which accomplishes some preferred image optimization. Previously, however, no simple (single) or complex (double or multiple) pulse sequence has been able to increase the relative signal intensity of nerve so that it is brighter than all other tissues in the body or limb cross section. Surprisingly, the inventors have discovered that there are certain novel ways of assembling complex pulse sequences wherein, even though the simple components of the sequence decrease the signal to noise ratio of nerve or decrease the signal strength of nerve relative to other tissues, the fully assembled complex sequence actually results in the nerve signal being more intense than any other tissue. In this fashion, the image conspicuity of nerve is greatly increased.

Thus, a first aspect of the present invention provides a method of selectively imaging neural tissue of a subject without requiring use of intraneural contrast agents, the method comprising subjecting part of the subject anatomy to magnetic resonance imaging fields, detecting magnetic resonance and producing an image of neural tissue from said electronic signal so that in said image, a nerve, root or neural tract of interest can be visually differentiated from surrounding structures.

It is important to realise that although previously, it has sometimes been possible to make a nerve stand out from immediately surrounding structures, it is the unique, very useful, and novel ability to make the nerve stand out from all other structures which is a significant advantage of the present invention. This is an important distinction in the area of 3-dimensional reconstruction since the use of gray-level gradient shading and surface rendering is difficult when applied to very small structures such as some nerves. By reducing all other structures below the intensity of nerve as described hereinbelow, it becomes possible to employ, among other techniques, simple threshold algorithms and, importantly, maximum intensity projection to achieve good quality 3D rendering for structures close in size to a single image voxel in the course of applying ray casting or other 2D or 3D projection methods.

It should be noted that in some cases, a region of interest can be selected within which the nerve is the brightest or most conspicuous (brightest or darkest) structure. Other criteria which may be applied are the achievement of a high nerve signal to muscle signal ratio (S_n/S_m) and/or a high nerve signal relative to fat (S_n/S_f). Where other tissues are collectively viewed as 'background,' a neurographic effect will exist where S_n/S_b is large enough as to make nerve readily identifiable. This is particularly useful when the residual signal from nerve after all other signals have been reduced, still maintains a useful level of S_n/Noise.

Where all non-nerve tissue can be reduced to relatively very low intensity, or indeed be caused to disappear entirely from the image it becomes readily possible to program a computer to identify the nerve locations in the anatomical structure and to correctly trace the course of the nerves between 2D image planes or through a 3D acquisition volume. The ability to correctly trace the course of a nerve through its anatomical relations and over the course of its various divisions and ramifications is a significant aspect of the invention. This is because a 2D image may demonstrate various bright dots representing the cross

tion of nerves. However, with other anatomical information deleted, it is often important to be able to reconstruct the nerve tree in order to correctly identify precisely which nerve is which in any given 2D section, 2D projection, 3D projection, rendering or perspective display, whether or not that display is susceptible to rotation on the computer screen to aid the user of the image.

Preferably, the image selectivity for nerves is provided by discriminating properties of water diffusion anisotropy or of proton fast exchange rates or of T_1 but optimally T_2 relaxation rates as will be described in more detail hereinbelow.

A second aspect of the present invention provides a method of selectively imaging neural tissue of a subject, the method comprising subjecting part of the subject anatomy to magnetic resonance imaging fields adapted to discriminate anisotropy of water diffusion or other special characteristic of neural tissue, detecting magnetic resonance to produce an electronic signal in accordance with said resonance and producing an image of neural tissue from said electronic signals.

Preferably, the imaged neural tissue constitutes the main, or even the only, structure visible. The imaged neural tissue may be selected and physically aligned tracts of neural tissue.

Neurographic imaging effected in accordance with the present invention utilises a set of special pulse sequence and program instructions to control the electronic equipment of an MRI scanner. For the imaging of fine nerve branches, the pulse sequences can be aided by the use of special signal and imaging coils placed near or around the portion of the body of greatest interest. The imaging can also be improved by the use of a phased array RF coil system in which the signal to noise is greatly increased and the image therefore benefits from a substantial improvement in spatial resolution or in retrieval of signal where various suppression techniques have been applied so that the remaining signal to noise would otherwise be too low to achieve useful images.

Neurographic imaging does not require the administration of any pharmaceutical agent. Indeed, since neurographic imaging makes nerves appear bright and isolated in an image, it then becomes far more informative to selectively black out one of the nerves by means of administering an intraneural pharmaceutical contrast agent.

Thus image neurography can be viewed as a way of effecting a process which rapidly produces an image of an entirely new kind, wherein that image can be examined for its anatomical information content, and wherein that image can be manipulated by the administration of pharmaceutical agents such as intraneural contrast agents or intravenously administered contrast agents or other types of contrast agents which have effects upon magnetic resonance signals.

The aforementioned intraneural nerve imaging pharmaceutical agents were designed to help in the diagnosis of nerve compressions and nerve compressions and nerve injuries, it was not anticipated that the nerves could be seen in relative isolation without administering any pharmaceutical. Indeed, users of such agents have acutely appreciated the need for some imaging technique which would synergistically render the effects of the intraneural agents into much more useful form, although neurography per se had not been appreciated as the solution to this problem, nor had any proposal to attempt to accomplish branching image neurography been made.

The fine spatial resolution required for creating detailed images of peripheral nerves, including their small distal ramifications and divisions, is well within the physical range of current clinical magnetic resonance imaging instruments, particularly when specially designed local signal and imaging coils are used.

The inventors have discovered that there are various different sets of pulse sequences and combinations of pulse sequences which can be used to unambiguously distinguish small nerves from neighboring structures of similar shape and location. This includes the combination of some existing sequences into new groupings for use in new situations as well as the design of new sequences which incorporate optimized features for the purpose of neurographic imaging.

The ideal 'neurographic image' is analogous to a subtraction angiogram (an image showing only blood vessels), but sharply highlights a nerve rather than a vessel. Such an image is most useful for confirming the identification of nerves in a given imaging plane or space as well as for locating nerve injuries and nerve compressions. Despite the well known existence of angiograms showing the entire vascular pattern in an anatomic regions, and despite the existence for many years of various magnetic resonance techniques which could have been applied to the creation of neurograms, and despite the lack of any feasible

thod for visualizing nerves in isolation, there has not previously been any way of creating neurograms.

An important obstacle to the invention of neurograms has been the difficulty of knowing with assurance that a given structure in an image plane actually is a nerve as opposed to some other structure similar in shape and location. The inventors have solved this problem by discovering a set of pulse sequences which can unambiguously prove that a given structure in an image is indeed a nerve. Using this tool, it was then possible to discover other simpler pulse sequences which achieved the same image result when applied to the same subject in the same scanner during an imaging session. In this fashion, by first confirming the nerve images, and by then using the firm data to cross check the results of other techniques useful for various reasons, it was possible to build up a collection of techniques capable of application for practicing the invention, e.g. for producing image neurograms with a magnetic resonance scanner.

The inventors have carried out experiments in which they tested imaging techniques which enabled them to selectively delete the signal from non-neural structures and also evaluated techniques which permitted relative enhancement of the image signal from nerve. One discovery was that neurographic imaging could be greatly aided by taking special advantage of the "anisotropic water diffusion" which is known to take place in muscle, in the central nervous system and in peripheral nerves. Stated simply, water diffusion occurs preferentially along the axial length of nerves, more than radially across the nerve tissue. This directional preference for diffusion may be detected by magnetic resonance imaging, more especially by proton nmr imaging. However, nmr utilising other magnetic resonance susceptible nuclei may also be used, e.g. ^{19}fluorine, ^{13}carbon, ^{31}phosphorus, deuterium or ^{23}sodium.

For a preliminary enhancement of the image of the nerves, it is preferable to apply a process to eliminate non-neural signals during the magnetic resonance imaging, for example by suppression of resonance signals from fat. Fat suppression may for example be effected by chemical shift selection or by selective water stimulation. Other means to achieve fat suppression include the Dixon technique and also STIR (short tau inversion recovery) which can be used for neurography.

The inventors have demonstrated that, under ideal image collection and pulse sequence circumstances, the diffusion coefficient of anisotropy in peripheral nerve is

greater than that in muscle, and that it was possible to collect appropriate diffusion weighted images after preliminary fat suppression in such a way as to generate image neurograms or to reliably identify nerves.

In the imaging method according to the present invention, it is preferred that magnetic diffusion weighted field gradients are applied in at least two different directions and the signals from the respective resultant resonances are subtracted to produce said discrimination of water diffusion anisotropy. Most preferably, the magnetic field gradients are applied in mutually substantially orthogonal directions.

It should also be noted that the inventors have discovered that there is a synergistic effect in which the application of fat suppression increased the apparent diffusional anisotropy of nerve. The data generated in this experiment revealed that when signal from fat and from short T_2 water was removed from an image, that the remaining signal derived in substantially greater amount from the anisotropically diffusing water.

	CHESS			
	Yes		No	
	⊥	∥	⊥	∥
Ulnar Nerve	29	<8	62	49
Median Nerve	30	<8	46	22
Muscle	14	8	18	12

This synergistic effect of fat suppression can also be viewed as a demonstration of a magnetization transfer effect. Irradiation of the protons on e.g. myelin lipids by the saturation pulse, then allows transfer of the saturation pulse to water molecules which are in close association with the lipid, where that water is demonstrated to be subject to relatively isotropic diffusion.

It is also possible in many anatomical regions to achieve adequate enhanced isolation of the nerve image by applying only a single diffusion gradient perpendicular to the long axis of the nerve at the site of interest. When this is adequate, then no subtraction need be carried out to produce the neurogram. The fat suppressed orthogonally diffusion weighted image can either be processed directly, or it can be subject to threshold processing

which will remove signals of lower intensity from non-neural tissue or from nerves with different long axis and direction of travel at the imaging location.

Similarly, in some regions of interest, it is possible to achieve adequate enhanced isolation of the nerve image by use of a spin echo fat suppression technique with a long TE (echo time) between 50 and 100 milliseconds or even longer where useful (see figure 14). This is is because after fat suppression, the dominant signal to suppress is from muscle. Since the T_2 of muscle is approximately 27 milliseconds while the T_2 of peripheral nerve is approximately 55 milliseconds (both as measured by the inventors) there is a factor of two difference between the two types of tissue. The inventors have used this technique at 1.9Tesla to produce images of one of the inventor's wrists in which nerves are brighter than any other structure in the image and which images are therefore susceptible for use in constructing neurograms.

When a phased array or other very high resolution imaging coil or MRI system is used for human imaging studies with this long TE sequence, the inventors have discovered another unanticipated and surprisingly beneficial effect. This sequence causes the individual nerve fascicles to appear much brighter than the perineurial tissue within the nerve but between the fascicles. Because of this, the nerve takes on the appearance of a multi-fascicled structure.

This is important for two reasons. Firstly, this enhances the diagnostic usefulness of the image since it makes it possible to observe and analyze the internal structure of the nerve for any evidence of disease. Secondly, this proves to be a very useful additional means of identifying nerves in a neurographic image. Other structures which are similar in size to nerve and which may appear bright in long TE sequence neurograms include vessels, lymphatics, lymph nodes, and small collections of adipose tissue, however none of these tissues have the internal fascicular structure typical of nerve and demonstrated by this technique. Therefore, this sequence and imaging result permit the unambiguous differentiation of nerve from other tissues in cross sectional images which is one of the key elements of neurography.

An additional measure which may be taken to improve the neurographic selectivity of long TE sequence neurograms is the application of vessel suppression in addition to the aforementioned fat suppression and muscle suppression. This may be accomplished in any one of several ways which include but are not limited to the following: 1) processing or

collecting the image in such a way as to produce a flow based MR angiogram (as by phase contrast or time-of-flight, or other such techniques) and then subtracting the angiogram from the long TE neurogram image; 2) using a short TE sequence to obtain bright vessels and dim nerves then subtracting this from a second image with long TE; 3) administration of an intravenous 'black blood' contrast agent, preferably but not necessarily of the 'blood pool' type including dysprosium-DOTA poly lysine or iron oxide type contrast agents, 4) use of carefully adjusted water suppression techniques such as FLAIR.

Yet another means of accomplishing the secondary nerve enhancement is by means of a magnetisation transfer pulse sequence after the fat suppression. Because of the relatively slow rate of exchange between the off-resonance relatively stationary protons in myelin sheath and the on-resonance mobile protons of axoplasmic water, there is a differential sensitivity between nerve and muscle when magnetisation transfer is applied. Other useful pulse sequences include modified versions of steady state free precession (SSFP) and magnetization prepared rapid gradient echo (MP-RAGE) and a variety of other image acquisition techniques.

Where motion sensitive sequences such as diffusion gradient techniques are used, the acquisition can be electively carried out with immobilization of the limb by the application of splints. Such equipment for enhancing neurography will also include immobilization splints which serve to maintain a uniform volume within an imaging coil and to minimize susceptibility artefacts at skin edges both of which measures serve to improve effective field homogeneity and uniformity of e.g. fat suppression. Such splints can include both a rigid component of plastic or some other non-ferromagnetic material and a component of some conformable substance such as a water containing foam capable of close application to the skin surface. One such splint arrangement involves a rigid component and a sack or bag of thin film plastic wherein the conformable substance is pumped into the sack to achieve the effect of both immobilizing the patient's limb or neck or other body part, and also of causing the thin film to become closely applied to the patients skin surface.

Still another means of practicing neurography is by optimizing sequences to be sensitive to the slow coherent flow of the endoneurial fluid. This provides a unique signal because of its proximal to distal direction of flow and because of its slow rate which can be monitored by techniques originally developed to distinguish diffusion from perfusion,

including velocity compensation by first order gradient nulling as well as others, which detect flow and can be optimized for very slow directional flow rates.

Where sites of nerve compression, section, laceration, or fibrosis are imaged, the alteration in endoneurial fluid flow and in axoplasmic flow can be detected by increase of signal intensity when T_2 based neurographic sequences or other neurographic sequences are used (see figure 16, 17, and 18).

The present invention also includes a method of diagnosis or physiological investigation comprising application to a part of the subject anatomy of an imaging method according to the present invention as hereinbefore described.

Various diagnostic applications of the method of the present invention may be better understood with reference to Figure 1 of the accompanying drawings, which shows a sectional view through a vertebra. The structures and conditions illustrated are denoted by the following reference numerals:-

9. Herniated Disc
10. Compressed Root
11. Spinous Process
12. Anulus Fibrosus
13. Nucleus Pulposus
14. Autonomic Ganglion
15. Ventral Root
16. Ventral Ramus
17. Transverse Process
18. Dorsal Ramus
19. Dorsal Root Ganglion
20. Facet
21. Dorsal Root
22. Extradural Fat
23. Root in Cauda Equina
24. Dural Sac
25. Cerebrospinal Fluid within Dural Sac.

In this diagram, the two features of interest are the left spinal root (10) and the left ventral root which are both in risk of compression from the herniating disc (9). Both nerves are travelling through fat (22) but are surrounded by bone (which could impair observation by an X-ray based technique) and are near the strong water signal of disc and of cerebrospinal fluid in the dural sac (25) and other inflamed tissue (which often diminishes image resolution and quality in generally used magnetic resonance techniques).

The structures of diagnostic interest (10 and 15) are small relative to the large number of other anatomic structures nearby. Also note that (10) and (15) are nearly perpendicular to each other. This very common imaging problem could now be approached by applying fat suppression, then selecting orientations for pulsed diffusion gradients which enhanced either the spinal root (10) or the ventral root (15) so that each could be clearly seen in a given image and carefully examined for evidence of compression or inflammation.

Other diagnostic applications include the following:-

1. Demonstrating the anatomy of peripheral, cranial, and autonomic nerves and nerve plexuses.

2. Demonstrating the anatomy of spinal roots, particularly, cervical, thoracic or lumbar spinal roots where they pass through fat at the foramina through which they exit the spinal canal.

3. Demonstrating the anatomy of spinal roots within the lumbar canal where they pass through quantities of extradural fat.

4. Examining cranial nerves for compressions by vessels or other structures which could cause trigeminal neuralgia (Vth nerve), hemifacial spasm or Bell's palsy (VIIth nerve), essential hypertension (Xth nerve) or other cranial nerve syndromes.

5. Demonstrating nerve, plexus or root compressions or injuries where abnormal changes in the direction, position, or other diffusional properties are caused by an injurious process, such as nerve transection, demyelinating diseases, peripheral neuropathies and crush injuries. These concerns apply similarly to monitoring the regrowth of nerves.

6. Exploring the location of tumours or other masses within the spinal cord where it is useful to know the position of cortico-spinal motor tracts or other functional white matter long tracts relative to some abnormality.

7. Demonstrating the anatomy of the optic nerve, an extension of the brain, where it passes through the peri-orbital fat other fat on its route to the retina.

8. Tract tracing within the brain in order to provide useful images for study by radiologists, surgeons or physicians. In particular, for identification of the location of areas of 'eloquent cortex' such as the motor strip, or speech related areas. This method involves the spatial identification of relevant areas of the thalamus or internal capsule and then following projecting tracts to the area of interest on the cortical surface, or identify regions of interest by reference to their connections with other areas on the cortical surface.

9. Tracing of nerves as they pass through tumours of low diffusional anisotropy. Such as the passage of the VIIth nerve through an acoustic neuroma in order to permit a surgeon to know the location of the nerve in or near the tumour and so to have the ability to avoid the nerve during surgery on the tumour.

10. Application of diffusion anisotropy imaging for the evaluation of diffuse axonal injury, as may occur in head injury.

11. In the evaluation of bone fractures and joint dislocations or dislocation/fractures in which surgical planning, management and fixation would benefit from knowing the course of the nerve in the region of the abnormal anatomy.

This invention can also be used to improve a number of different treatments of the human body. In one aspect, the production of neurographic images for publication in an anatomical atlas can provide general guidance for a surgeon. Comparable images of the patient will rapidly identify any anomalous nerve courses in a patient who is meant to undergo surgery for some condition. In this fashion, the surgeon can modify his technique to reduce the risk of injury to nerves which happen to be in the field of surgery. Similarly, a neurographic map of an individual patient's skin and cutaneous nerves will help the surgeon to plan incisions which avoid the very common complication of accidental transection of cutaneous nerves in the course of routine surgical incision to reach structures below the skin.

A most important example of this concerns the recurrent laryngeal nerve. In any surgery in the neck, such as a carotid endarterectomy to remove stroke producing plaque from the internal carotid artery, or an anterior cervical discectomy to relieve a cervical root compression, or an operation for cancer in the neck, or other neck surgeries, one of the most common complications is accidental crush or transection of the recurrent laryngeal nerve which results in possibly permanent paralysis of one or both sets of vocal cords. Optimally, a pre-operative neurographic image could demonstrate the course of the recurrent laryngeal nerve so that the surgeon could more effectively avoid it, or more easily identify and protect it during surgery.

In a further aspect, the neurographic image can be collected in conjunction with other tissue selective images to assemble a three dimensional image with various identified components. The inventors have collected an image with nerve enhancement, then modified conditions to enhance the blood vessels. This shows the physical relation between the nerves and vessels at various locations which is again very helpful for guiding a surgeon in the treatment of nerves, the treatment of vessels or in the treatment of other structures near the nerves and vessels.

Similarly, an image can be produced in which the fat component is selectively demonstrated and remaining tissues suppressed. This emphasises the appearance of skin, adipose collections, and also of bone (in many locations) due to the presence of marrow (see figure 8). When such an image is collected, assigned a color, then shown transparently in the same three dimensional image construction as the neurogram, useful information is provided on the relation between nerves and bones. This is most important in the evaluation of bone fractures and in the planning of their treatment. Similar considerations apply in the planning and carrying out of treatment of injuries to joints.

In yet another aspect, thus, the invention can be viewed as a novel and fundamental advance which makes possible the construction of various automated surgical guidance and surgical treatment systems. In one embodiment, e.g. the patient's arm is placed in a simple splint across one joint wherein the splint carries certain fiduciary markers of e.g. small water filled beads. An image neurogram is then collected and a computer program generates numerical coordinates which describe the position of the nerves along their courses with reference to the three dimensional location of the fiduciary markers in the splint. An additional fat selective image to show bones may be then be taken, or the patient may be

brought to a CT scanner for preparation of a bone image while wearing the same splint, but with reference to CT X-ray visible fiduciary markers such as chalk or iodine solution.

To carry out the neurogram guided surgery, a device is attached to the splint which may comprise an electronically monitored articulated arm system or a rigid coordinate based positioning system, or even a laser based position system. At this point, the treatment proceeds either by direct reference to a listing of the spatial coordinates of the nerve relative to the splint, or, preferably, under direct guidance of a computer based system. The computer is able to match the position of the articulated arm or laser focus or other positioning system to its internal image of the spatial location of the nerves or other structures. A three dimensional on-screen image may be generated which shows the course of the nerves and the position of the end of the articulated arm.

By analogy, such a neurogram guided treatment system can be used with fiduciary markers on the head or face in relation to nerves of facial sensation or movement, or can be used in relation to the iliac crests and lumbar vertebral spinous processes to locate lumbar nerve roots. The use of such a technique in the spine will be most helpful for reducing one of the most common complications of cervical, thoracic or lumbar spine surgery which is the problem of doing a good operation but at the wrong level, e.g. inadvertently decompressing the lumbar 3/4 root when the symptomatic compression was actually at the lumbar 4/5 root. For spine work, the original image can be collected with a strip of fiduciary markers taped to the back and marked on the skin with a marker to allow location by the guidance device at the time of surgery.

Such neurographic guidance can be used for percutaneous needle biopsy of lesions, or for the placement of more elaborate percutaneous systems such as ultrasonic or other mechanical devices used to remove tissues as for discectomies, for introduction of laser/suction systems, for the placement of RF lesioning devices used in such procedures as gangliolysis of the fifth cranial nerve, for the placement of probes to carry out deep tissue localized drug administration, diathermy, cryotherapy or other physical or mechanical techniques. This sort of data may also be used to guide the passage of rigid endoscopes through solid tissues or to guide the placement of directable flexible endoscopes.

It is additionally noted that fiduciary, stereotaxic or computer guided techniques are not in and of themselves crucial to the useful application of neurographic data to

therapeutics. For instance with the use of high speed MRI data collection sequences such as echo planar imaging, it is possible to rapidly update images. When the resulting images are projected back into the MR suite, the surgeon or radiologist may observe an appropriately labelled, non-magnetic probe in realtime as it is advanced into the body. With slower image collection, the probe or device is advanced in steps as a series of images are taken. Here, the neurographic image simply serves to guide the surgeon or radiologist by providing apparent vision of sensitive neural tissue inside opaque, solid body structures, much as fluoroscopy is used currently, but in this fashion, also permitting the interventionalist to know where nerves are located.

Still another aspect of this neurogram directed positioning system includes the use of a stylus tip at the end of a robotic arm in which the stylus can detect electrical activity of nerves. Currently, there are surface detectors of electrical fields and also magnetic detectors of nerve activity and these are positioned manually based on general knowledge of standard anatomy. In the method of the invention, the computer driven stylus carries an electrical or magnetic sensor for nerve activity, however the detector can be precisely positioned relative to a variety of useful nerve locations by interactive use of the three dimensionally referenced neurogram data.

The first aspect of the invention also provides an apparatus for selectively imaging neural tissue of a subject without requiring the use of neural contrast agents, the apparatus comprising means for subjecting part of the subject anatomy to magnetic resonance fields, means for detecting magnetic resonance to produce an electronic signal in accordance with said resonance and means for producing an image of neural tissue from said electronic signal so that in said image, a nerve root or neural tract of interest can be visually differentiated from surrounding structures.

The second aspect of the present invention also finds expression as an apparatus for imaging neural tissue of a subject, the apparatus comprising means for subjecting part of the subject anatomy to magnetic resonance fields adapted to discriminate anisotropy of water diffusion, means for detecting magnetic resonance to produce an electronic signal in accordance with said resonance and means for producing a selective image of neural tissue of interest from said electronic signal.

Preferably, any apparatus according to the invention also comprises a coil for application of a radiofrequency field to said anatomy part and/or for detection of a

resonance signal, wherein said coil is configured and dimensioned to fit closely over said anatomical part.

Conveniently, the coil is a solenoid coil or surface coil and is configured and dimensioned to fit closely over a human limb, shoulder, chest, pelvic region, head, neck or back.

In principle, selective imaging of part of any other object or subject may be effected using magnetic resonance if that subject or object exhibits diffusion anisotropy in any part thereof. Thus, in medicine, for example a part of the cardiovascular system could be imaged in similar fashion. However, the technique could also be applied to rock strata, plants etc if diffusion anisotropy occurs in same.

Thus a third aspect of the present invention provides a method of selective imaging, the method comprising observing diffusion anisotropy.

The third aspect of the invention also provides a magnetic resonance apparatus for selective imaging, said apparatus being adapted to discriminate diffusion anisotropy.

The present invention will now be explained in more detail by the following description of a preferred embodiment and with reference to the accompanying drawings, in which:-

Figure 1 shows a section through the lumbar spinal canal and a lumbar vertebra with a herniated disc to indicate the size and location of the nerves and their surrounding structures ;

Figure 2 shows a magnetic resonance imaging apparatus for use in accordance with the present invention;

Figure 3 shows an example of pulse sequencing for operating the apparatus shown in Figure 1;

Figure 4 shows a diagram of a transverse section of the upper fore-arm of a rabbit based on the fat suppressed image shown in Figure 5. 201) triceps muscle, 202) ulnar

nerve, 203) brachial veins, 204) median nerve, 205) radial nerve, 206) humerus, 207) cephalic vein, 208) biceps muscle;

Figure 5 shows a fat suppressed image in which black represents highest intensity of resonance signal;

Figure 6 shows the effect of application of a perpendicular pulsed gradient renders the nerves as the highest intensity features in the image; and

Figure 7 shows the effect whereby reorienting the gradient parallel to the long axis of the nerve has a relatively greater effect in reducing the nerve signal than that of the muscle.

Figure 8 shows the difficulty of unambiguously identifying a nerve in a standard spin echo image or even in an image using STIR fat suppression alone.

Median nerve contrast study by solenoid coil MRI. All images are from a single slice of rabbit upper arm. Images B & C are spin echo studies. Note that the marrow (3) appears shifted out of the humerus by chemical shift effects. Similar shifts are seen at (4), and serve at (5) to leave two bright structures in a gap between triceps and biceps. Image A is collected with a STIR (short tau inversion recovery) sequence which reduces the marrow signal, and also helps identify structure (1) as a nerve while structure (2) disappears.

Based on this identification, the nerve (1a) is compared to non-neural structure (2a) and is seen to lose intensity in the six hour interval between images B and C reflecting transport of a WGA-ferrite contrast agent injected into forearm muscles.

Figure 9 shows the effects of increasing gradient strengths in a CHESS image with the use of threshold detection to yield an unambiguous localization of the nerves.

The images show a single image slice of the upper arm of a rabbit. The four images were acquired by a single interleaved sequence using a three turn solenoid coil in a 4.7 T SISCO instrument. Fat suppression is by CHESS and the diffusion weighted gradient is applied perpendicular to

the long axis of the arm. At Grad = 0 Gauss/cm, fat, bone, marrow, skin, and vessels are already removed from the image. As gradient strength is increased above 5 G/cm, the muscle signal begins to fade and at 7 G/cm ligaments, lymphatics and other remaining structures also drop out leaving only the nerves as bright objects. At the top of each image is a signal intensity trace along a horizontal line through the radial nerve.

U = ulnar nerve, Me = Median nerve, Mu = musculocutaneous nerve, R = radial nerve, tr = position of trace line.

Figure 10 shows a computer engaged in neurogram display and control of an articulated or robotic stylus. 10.01 is the image of the articulated arm, 10.02 is an image of an arm bone, and 10.03 is a three dimensional image of a nerve in the arm. Movement of the stylus by the surgeon permits the computer to display the position of the stylus in relation to a stored image of the patient's anatomy. Alternately, the computer can be used to guide a computer operator in remote control of the stylus.

Figure 11 shows the use of the neurogram guided system in an operating room. 11.01 is the stylus device and includes a unit which monitors the location of the tip of the stylus as well as monitors connected to the arm splint. The tip of the stylus can be used as a pointer only, or can have a surgical laser or similar therapeutic device, or can carry a magnetic detector of nerve activity for monitoring nerve function at precise locations. 11.02 is the patient on the surgical table. 11.03 is the locational splint - it is scanned while on the patient's arm prior to surgery and its fiduciary markers are used to create a three dimensional coordinate system defining the location of the patient's nerves relative to the splint. In the figure, the splint is reapplied in the operating room and then connected to the stylus device to provide the link with the computer's model of the three dimensional space.

Figure 2 shows an example magnetic resonance imaging apparatus 101 suitable for use in the present invention. It comprises a magnet 103 and a tuned radiofrequency (rf) coil 105 for excitation of the nucleus and detection of the required signal (separate transmit and receive coils may also be used). This coil is placed over a limb 107 under investigation.

One pair of a set 109, 111 of three pairs of coils used to generate a magnetic field gradient over the sample region. A computer 113 is used to control and synchronise the necessary electronic devices of the MRI and process to display the acquired data. An

interface bus 115 is arranged between the computer and the electronic devices. A device 117 is used to generate the required radiofrequency pulse shapes. Another device 119 is used to generate the required gradient pulse shapes.

The device 117 is connected to a high power radiofrequency amplifier 121 for the rf pulses. Another amplifier 123 (one of three) is connected to the device 119 and has an output arranged to drive the gradient coils.

A duplexer 125 is arranged to steer the high power rf pulses from amplifier 121 to the coil 105 and steer the very low signals received by the coil to a preamplifier 127 for the received NMR signals. A mixer 129 is connected to the preamplifier to transform the high frequency nmr signals to low frequency signals by mixing with signals from a digitally controlled rf oscillator 131. The output of the mixer is connected to an analogue-to-digital converter 133 via a low pass filter 135.

Operation of the apparatus shown in Figure 2 to perform an imaging method according to the present invention may be understood better from the pulse sequences illustrated, by way of example only, in Figure 3.

Frequency selective pulses A,B and C selectively excite the nuclear spins of the fat molecules and the gradient pulses a, b, and c (along axes X,Y and Z respectively) dephase these spins thereby minimising the contribution of the fat signals to the final image. This is the known fat suppression technique using CHESS (Chemical Shift Selective) pulses.

A spin echo signal F, is generated by the combination of the radio-frequency excitation pulse D and refocussing pulse E. The pulsed gradients d to g are the imaging gradients used to encode the signal F in the usual manner such that an MRI image may be constructed. The sequence may be used to generate images from contiguous slices of the sample/patient under investigation.

The echo signal F, and therefore the pixel intensity in the constructed image is made sensitive to the spatial diffusion of the water molecules by the addition of the pulsed gradients h and h' known as the "diffusion sensitizing gradients". Spatial anisotropy in the molecular diffusion is determined by comparing two or more images acquired with the diffusion sensitizing gradients oriented along different axes. The images are obtained in

such a way to minimise motion artefacts by acquiring the data for the different diffusion sensitizing gradients in an interleaved manner.

In the case of a major axis of known diffusion anisotropy (e.g. a nerve tract) a simple 'image neurogram' may be generated by simply subtracting the appropriately scaled image obtained with the diffusion sensitizing gradient oriented parallel to the nerve tracts from a scaled image obtained with the diffusion sensitizing gradient oriented perpendicular to the nerve tracts.

If the major axis of diffusional anisotropy is not known, a plurality of images are acquired with different orientations of the diffusion sensitizing gradients. The image data can then be processed to give a parameter associated with each pixel (or voxel in a 3D data set) which is a measure of the diffusional anisotropy at that point reflecting both magnitude and direction.

The method used in this embodiment first carries out the fat suppression technique which maintains excellent image resolution, or uses a sequence which selectively excites only the water signal so that fat does not contribute to the final image and then, within the same pulse sequence, optionally includes an oriented pulsed gradient for selective incorporation of information from diffusion anisotropy.

The various parts of the pulse sequence are selected so as to optimally destroy as many other signals as possible other than that of nerve as shown in Figure 6. Then, optionally, a second sequence is carried out which selectively destroys the nerve signal as by for instance, rotating the diffusion gradient orientation to be parallel rather than perpendicular to the nerve as shown in Figure 7.

The effect of these manoeuvres is to produce two images, the first of which shows up the nerve relatively brightly, and the second of which selectively destroys the nerve signal. When these two penultimate images are then mathematically or photographically, or optically subtracted from one another, and optionally divided by the signal information from a fat suppressed T_2 weighted spin echo sequence (e.g. using the aforementioned CHESS technique), the result is one example of a neurogram (see figure 15). Optimally, the non-neural tissues are carefully balanced in intensity before undertaking the subtraction.

An alternative approach would be to use pulsed gradients oriented in each of a plurality of or into specially created axes suitable to the imaging task. In this fashion, it is possible to determine a parameter which characterised the diffusion coefficient anisotropy for each voxel in the image, including both magnitude and direction. This parameter can be rendered to produce a neurographic image for good image registration.

To optimize the technique where data processing requires the manipulation of the image data on a point by point basis between a plurality of image data sets, the image sequence can be modified to interleave the different sequences and so to minimise any motion artefact which could degrade the accuracy of the final image when the different sequences are collected at times separated by several minutes. Furthermore the image sequence can be synchronised to respiration or to the heartbeat to additionally reduce the effects of motion. It is also possible to carry out the signal acquisition using a so called "three dimensional" imaging sequences processed by using a 3D Fourier transform.

Images were obtained with a 4.7 Tesla, 33cm bore SISCO system fitted with a 10 Gauss/cm high performance auxiliary gradient insert (12 cm inner bore). A three-turn solenoid coil (2.5 cm in length and 3cm in diameter) was placed around the upper portion of the forelimb of 2 - 2.5 kg rabbits. The animals were maintained under balanced continuous intravenous infusion of an anaesthetic mixture containing 1 mg of medazolam, 1.5 mg of fluanisone and 50 μg of fentanyl per ml at rates of 4 to 10 ml/hr to achieve a deep anaesthesia minimising motion artefacts from respiration.

A specially modified multislice spin echo imaging sequence (TE=40 ms, TR=1 sec) was adjusted to provide fat suppression (CHESS) and to accommodate diffusion weighting of images. This set of modifications allows operator control of the strength of the gradients and allows various strengths and orientations to be inserted into 'slots' or reserved times within the common base sequence. After an initial image with fat suppression only, there is next collected one image with diffusion gradients perpendicular to the image plane and then one image with diffusion gradients parallel to the image plane.

The CHESS sequence consisted of a 3 millisecond (ms) gaussian pulse for selective excitation of fat followed by a 5 Gauss/cm dephasing gradient of 3 ms duration performed 3 times with orthogonal gradients prior to each spin echo sequence. For diffusion weighting, pulsed gradients of strength Gi=10 G/cm, duration ∂=7 ms, and separation Δ=20 ms, were symmetrically placed about the 180° pulse. Transverse images

(nerves primarily orthogonal to image plane) with slice thickness of 2 mm were obtained for a 4 cm field of view with 256 phase encoding steps. Image data was zero filled to 512 points to give 78μm in plane resolution.

It is noted that the high 'b' value reflecting the strength of the diffusion gradient used can be achieved by varying not only the strength of the gradient but also the duration of the gradient. In this fashion, the same b value can be obtained at a lower gradient field strength when the gradient is applied over a longer period of time.

Simple spin echo images of limb anatomy proved inadequate for definitive identification of peripheral nerves because the nerves are typically surrounded by the high intensity signal from fat deposits in the intermuscular spaces. Further, there are a variety of structures similar to nerve in size and shape which follow similar routes.

However, it was found that the fat surrounding nerves is actually beneficial for nerve identification, because in a fat suppressed image, a relatively high intensity nerve signal stands out sharply within the very low intensity space left behind by the suppressed fat signal as shown in Figure 5.

Under these conditions the phenomenon of diffusion anisotropy was applied to the problem of nerve image enhancement and shown to be exceedingly effective (see Figure 4 to 7). Apparent diffusion coefficients perpendicular and parallel ($D_{\perp}$, $D_{||}$) were calculated from average pixel intensity measurements over the region of interest (ROI) from each of the three different images in a given set. Calculation employed the formula (Intensity = $A_0.\exp[-TE/T_2].\exp[-bD]$, attenuation factor $b=\gamma^2 Gi^2 \partial^2[\Delta-\partial/3] = 61.9\ 10^3$ sec/cm^2). .

Apparent Diffusion Coefficients (10^{-5} cm^2/sec)

	Muscle	Median Nerve
$D_{\perp}$	1.2	0.98
$D_{||}$	1.8	2.3
$D_{||}/D_{\perp}$	1.5	2.35

This example demonstrates that fat suppression by CHESS enhances the visualization of peripheral nerves so that when different diffusion gradient orientations are incorporated in secondary segments of the imaging pulse sequence, the ultimate yield is a far larger relative change in intensity in the nerve signal than in muscle.

This intensity change then provides the basis for an image subtraction technique to achieve relative nerve image enhancement. The various subtracted or divided nerve images are then assembled mathematically by routine reconstruction techniques into a three dimensional image. Thus the objective of assembling three dimensional neurograms is conveniently achieved.

In yet another example, the inventors have obtained neurographic images in a human patient who has a nerve graft. Images were obtained in a commercial 1.5 Tesla

magnetic resonance imaging system (Signa, system 5.2 software release, GE Medical Systems) with standard 1Gauss/centimeter gradients and a specially built phased array RF coil system. A fast spin echo sequence with a TR of 5000 ms, TE of 102 ms, and 8 echo train was used with fat suppression and spatial RF pulses for vessel suppression. Two axial series were performed using a two dimensional fourier transformation. The first series consisted of 24, 5mm thick sections, 512 x 512 matrix, 1mm skip, and 1 nex. The second series consisted of 41, 3 mm thick axial sections 256 x 256 matrix, 0 mm skip and 2 nex. The field of view was 18 cm and acquisition time was 10.6 minutes for both series.

Images from the second series were post processed by selecting an elliptical region of interest of approximately 2 cm in diameter around the sciatic nerve in each of the sections. Projectional images were obtained using a maximum intensity projection (MIP) algorithm (IVI, GE Medical Systems). This resulted in a neurogram showing the interface between the tibial component of the sciatic nerve and a surgically placed sural nerve graft (see figures 16, 17, and 18). In this case, a region of interest around the nerve was selected by the inventors so that a neurogram could be generated without using vessel suppression.

As an additional, previously unknown, unanticipated, and indeed surprising benefit arising from this technique, we found that our imaging protocol depresses the signal from tissues within the nerve between and among the fascicles so that the individual fascicles of the nerve stand out in sharp profile (figures 16 and 17). This unique internal fascicular organization is particularly helpful in distinguishing nerve from blood vessels, lymphatics, lymph nodes and collections of adipose tissue which may have similar shape, location, and intensity in the cross sections. This makes neurographic selectivity possible even when the conspicuity or signal intensity alone does not permit tissue based nerve identification since it establishes the appearance of a unique neural appearance in an image.

To follow nerves or CNS neural tracts it is important to provide a technique which is not limited to use in strictly orthogonal planes. As a nerve or neural tract curves or turns, the direction in which the diffusion anisotropy coefficient is greatest will gradually shift from one plane or axis to another. It may therefore be helpful to provide an algorithm which can combine information from anisotropy measurements in three orthogonal axes in order to observe the diffusion anisotropy independent of its degree of alignment with any individual axis.

In this example, a vector analysis is used to obtain images which combine information from the three orthogonal diffusion-weighted images. Brain scans were made of monkeys (*Macaca fascicularis*) weighing 2-2.5 kg by performing diffusion imaging (spin-echo) on a General Electric CSI II Imager/Spectrometer (2 Tesla, equipped with actively shielded gradients). The acquisition parameters were: TR 1000 ms: TE 80 ms; diffusion gradient duration 20 ms; diffusion gradient separation 40 ms; and four slices of thickness 4mm were imaged. At each imaging session, four multi-slice sets were acquired: zero diffusion gradient (B0) and diffusion gradients in the X (BX), Y (BY), and Z (BZ) orthogonal directions at 5 Gauss/cm. Conventional T_2-weighted images (8 slices) were used to reproducibly select the diffusion image planes.

The image intensities from the diffusion images were used to create new images, calculated on a pixel by pixel basis, using the following vector equations:

(1) $(\text{Vector length})^2 = BX^2 + BY^2 + BZ^2$

(2) diffusion vector angle between BX and BY = arctan (BY/BX)

(3) diffusion vector angle between BX and BZ = arctan (BX/BZ)

(4) diffusion vector angle between BY and BZ = arctan (BY/BZ)

Vector length images (figure 12) and arctan images such as the arctan (BY/BZ) image shown in figure 13 were generated in this fashion. Where vector analysis is used with diffusion weighting to evaluate CNS lesions, the vector length images will be more sensitive to water diffusion changes where all three orthogonal images change in the same way, while the vector angle images should be sensitive to changes in anisotropy between two orthogonal directions. In these images, a lesion caused by experimental allergic encephalomyelitis induced by myelin basic protein is demonstrated by its departure from the diffusional anisotropy and hence vector length decreases (fig. 12) and image intensity changes accentuated in particular vector angle images (fig. 13).

The use of vector analysis algorithms of this sort, or involving the treatment or coordinate transformation of MR diffusional anisotropy data with tensors of various rank can improve the generality and flexibility of neurographic imaging. The example described above demonstrates that by the application of tensor and/or vector analysis methods such as

algorithms similar to those developed for the evaluation of e.g. magnetic, thermal, or structural anisotropy data, it is possible to greatly improve the flexibility and generality of image techniques for neurological diagnosis.

Such techniques can also be used to follow continuous serial changes in the direction of maximum anisotropy of a nerve or neural tract as it travels along its natural course. Alternatively, such data can be managed by collecting data of the direction of maximum anisotropy for any given voxel and then applying voxel connection routines to follow the course of the nerve or neural tract of interest.

It is further worth noting that the creation of neural tract CNS neurograms can be used as a means of guiding stereotactic surgery in the brain. Currently, such techniques are guided by reference to structures visible by virtue of their tissue imaging characteristics such as T_1 or T_2. Use of CNS neurogram will allow the introduction of information concerning connections or relating to specific tracts of interest which may travel in or among other tracts from which they cannot be differentiated by means of other imaging techniques.

In the light of this disclosure, modifications of the described embodiment, as well as other embodiments, all within the scope of the present invention as defined by the appended claims, will now be apparent to persons skilled in the art.

CLAIMS

1. A method of selectively imaging neural tissue of a subject without use of neural contrast agents, the method comprising subjecting part of the subject anatomy to magnetic resonance imaging fields, detecting magnetic resonance to produce an electronic signal in accordance with said resonance and producing an image of neural tissue from said electronic signal so that in said image, a nerve or root or neural tract of interest can be visually differentiated from surrounding structures.

2. A method of selectively imaging neural tissue of a subject, the method comprising subjecting part of the subject anatomy to magnetic resonance imaging fields adapted to discriminate anisotropy of water diffusion, detecting magnetic resonance to produce an electronic signal in accordance with said resonance and producing an image of neural tissue from said electronic signal.

3. A method according to claim 2, wherein magnetic diffusion weighted field gradients are applied in at least two different directions and the signals from the respective resultant resonances are subtracted to produce said discrimination of water diffusion anisotropy.

4. A method according to claim 3, wherein said magnetic field gradients are applied in mutually substantially orthogonal directions.

5. A method according to any of claims 2-4, wherein a process to eliminate non-neural signals is applied during magnetic resonance imaging.

6. A method according to claim 5, wherein the process comprises suppression of resonance signals from fat.

7. A method according to claim 6, wherein said suppression is effected by chemical shift suppression.

8. A method according to claim 6, wherein said suppression is effected by selective water stimulation.

9. A method according to claim 5, wherein the process comprises magnetisation transfer.

10. A method according to any of claims 2-9, which method utilises proton magnetic resonance.

11. A method according to any of claims 2-10, wherein the image is a three dimensional image.

12. A method of diagnosis or physiological investigation comprising application to a subject of a method according to any preceding claim.

13. A method of selective imaging, the method comprising observing diffusion anisotropy by magnetic resonance.

14. An apparatus for imaging neural tissue of a subject, the apparatus comprising means for subjecting part of the subject anatomy to magnetic resonance fields adapted to discriminate anisotropy of water diffusion, means for detecting magnetic resonance to produce an electronic signal in accordance with said resonance and means for producing an image of neural tissue from said electronic signal.

15. An apparatus according to claim 14, further comprising a coil for application of a radiofrequency field to said anatomical part and/or for detection of a resonance signal, wherein said coil is configured and dimensioned to fit closely over said anatomy part.

16. An apparatus according to claim 15, wherein said coil is a solenoid coil or surface coil and is configured and dimensioned to fit closely over a human limb, shoulder, chest, pelvic region, head, neck, or back.

17. An apparatus for selectively imaging neural tissue of a subject without use of neural contrast agents, the apparatus comprising means for subjecting part of the subject anatomy to magnetic resonance fields, means for detecting magnetic resonance to produce an electronic signal in accordance with said resonance and means for producing an image of neural tissue from said electronic signal so that in said image, a nerve or root or neural tract of interest can be visually differentiated from surrounding structures.

18. A magnetic resonance apparatus for selective imaging, the apparatus being adapted to discriminate diffusion anisotropy.

19. A method of imaging neural tissue, the method being substantially as hereinbefore described with reference to any one of the accompanying drawings.

20. An apparatus for imaging neural tissue, the apparatus being substantially as hereinbefore described with reference to any one of the accompanying drawings.

21. A method of prophylaxis or treatment of a condition in a mammal comprising subjecting said mammal to magnetic resonance neurography.

22. A method of prophylaxis or treatment of a condition in a mammal comprising subjecting said mammal to magnetic resonance neurography without applying a contrast agent to said mammal.

22. A method of prophylaxis or treatment of a condition in a mammal comprising subjecting said mammal to magnetic resonance neurography by using the magnetic resonance to discriminate anisotropy of water diffusion.

23. Use of magnetic resonance neurography for prophylaxis or treatment of a condition in a mammal.

24. Use of magnetic resonance neurography for prophylaxis or treatment of a condition in a mammal without applying a contrast agent to said mammal.

25. Use of magnetic resonance neurography for prophylaxis or treatment of a condition in a mammal by using the magnetic resonance to discriminate anisotropy of water diffusion.

26. A method of designing or developing pulse sequences for the collection of magnetic resonance data with selective nerve enhancement wherein diffusion gradients or pairs of differently oriented diffusions gradients are used to test or further develop the pulse sequence.

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27. A method for making a set of measurements of the peripheral, cranial, or autonomic nerves in a living human body, wherein the set of measurements comprises a description of the course of the nerves through three dimensional space, or of the x,y coordinate of any nerve in any given cross sectional plane through the body.

28. A method according to claim 27 wherein this description of the nerves is collected together with an external grid or frame or splint containing fiduciary markers so that the coordinates of the nerves can be defined with regard to the position of the fiduciary markers whenever the grid or frame or splint is properly positioned with regard to the body section or limb from which the neurographic data is collected

29. A method according to claims 27 or 28 wherein this description of the nerves is used to generate an image on a computer screen showing the nerve or nerves in either two or three dimensions.

30. A method according to claims 27 - 29 wherein this description of the nerves is used by a computer in correlation with a robotic arm so that an image can be generated showing which nerves the robotic arm is near.

31. A method according to claims 27 - 30 wherein this description of the nerves is is used by the computer to draw or to guide the drawing of the course of a superficial nerve upon the skin surface whether or not any image is generated on a computer screen.

32. A method according to claims 27 - 31 wherein this description of the nerves is is used by the computer to guide a robotic arm, or laser, or other three dimensional positioning device in order to reach or follow a nerve inside the living human or mammal body.

33. A method according to claim 32 wherein the purpose is to permit the use of the computer to aid in surgical therapy or diagnosis by providing positional information or direct guidance to a physician or surgeon.

34. A method according to claim 32 wherein the purpose is to permit the use of the computer to aid in surgical therapy or diagnosis by operating a surgically effective device under computer guidance.

35. A method according to claim 34 wherein the surgically effective device is a laser, or ultrasonic, or cryogenic, or magnetic, or electric or electronic, or heat generating or mechanical device useful for surgical therapy.

36. A method according to claims 27 - 30 wherein this description of the nerves is is used by the computer to aid in the operation of an external lithotripsy device.

37. A method according to claim 11 wherein a long echo time (TE) is used to provide relative nerve enhancement or increased conspicuity whether or not any diffusion weighting is used.

38. A method according to claim 1 or 2 in which only a single diffusion weighted pulse is used, directed orthogonal to the long axis of the nerve or nerves.

39. A method according to claim 11 or 38 in which a threshold technique is used to help remove non-neural signals.

40. A method according to claim 11, or 37 - 39 wherein the water of the endoneurial fluid is selectively imaged.

41. A method according to claim 11 or 37 - 40 in which fat suppression is used to increase the apparent degree of diffusional anisotropy of nerves.

42. A method according to claim 11 or 37 - 41 for assembling neurographic data into a three dimensional image.

43. A method according to claim 42 wherein maximum intensity projection methods are used to create the three dimensional image.

44. A method according to claim 42 or 43 wherein a system of rules or algorithms based on the normal anatomy of nerves is used to aid a computer in the construction of a two or three dimensional neurogram based on raw neurographic data.

ABSTRACT

IMAGES APPARATUS AND METHODS

In an apparatus and method for imaging neural tissue, a part of anatomy of a subject is subjected to magnetic resonance imaging fields. The fields are adapted to discriminate water diffusion anisotropy. Resonance signals are processed to produce the required image.

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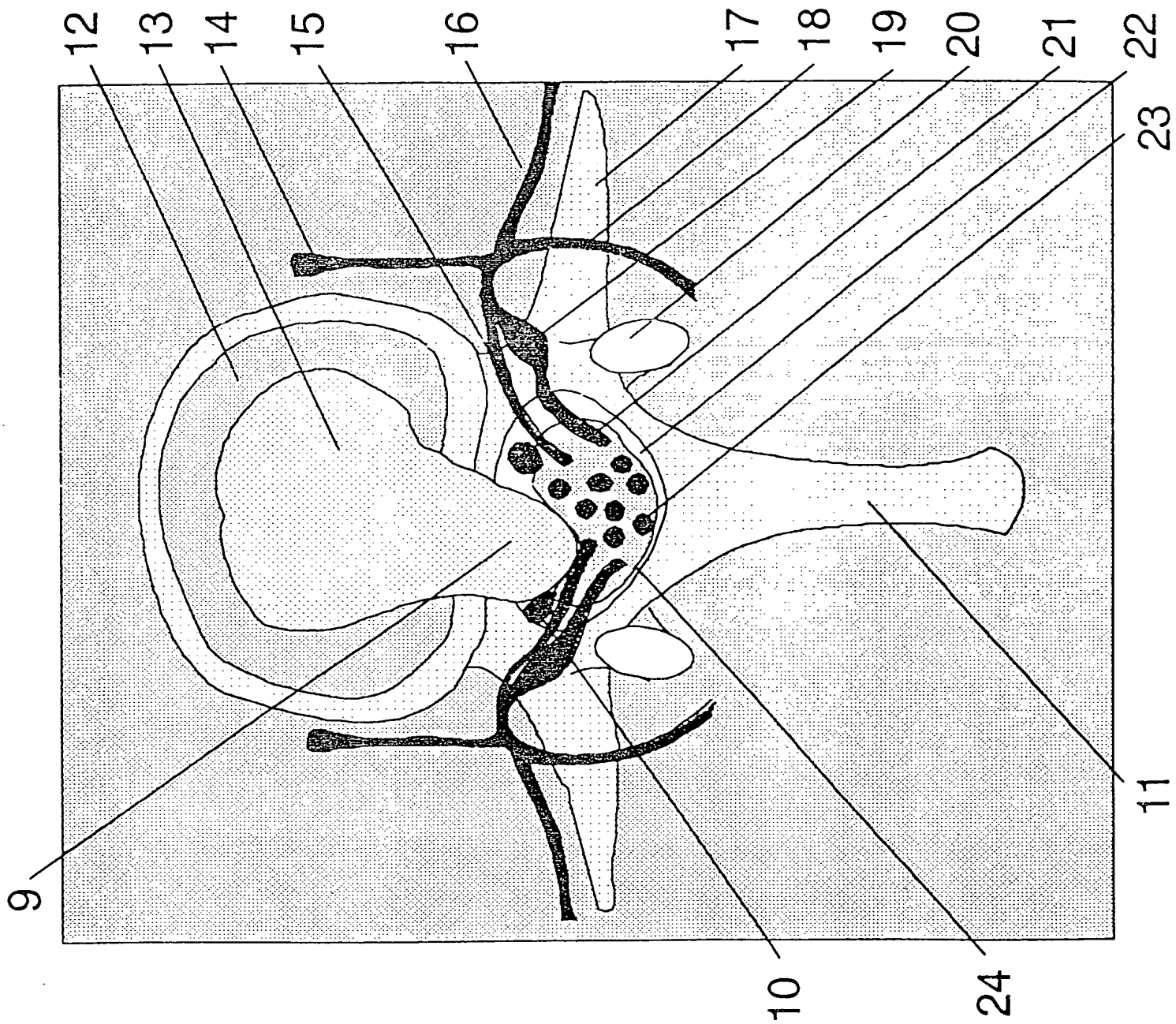

FIG 2

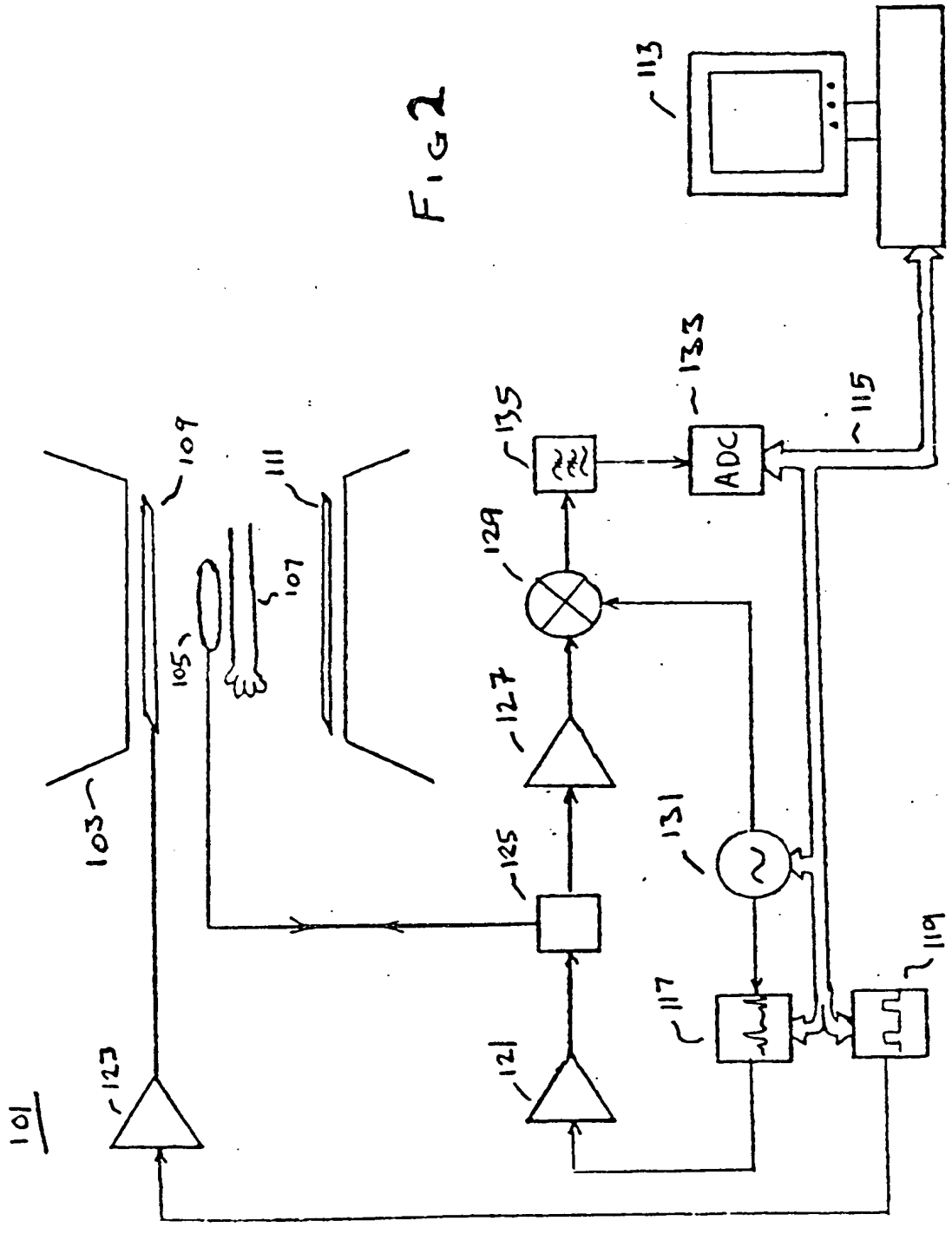
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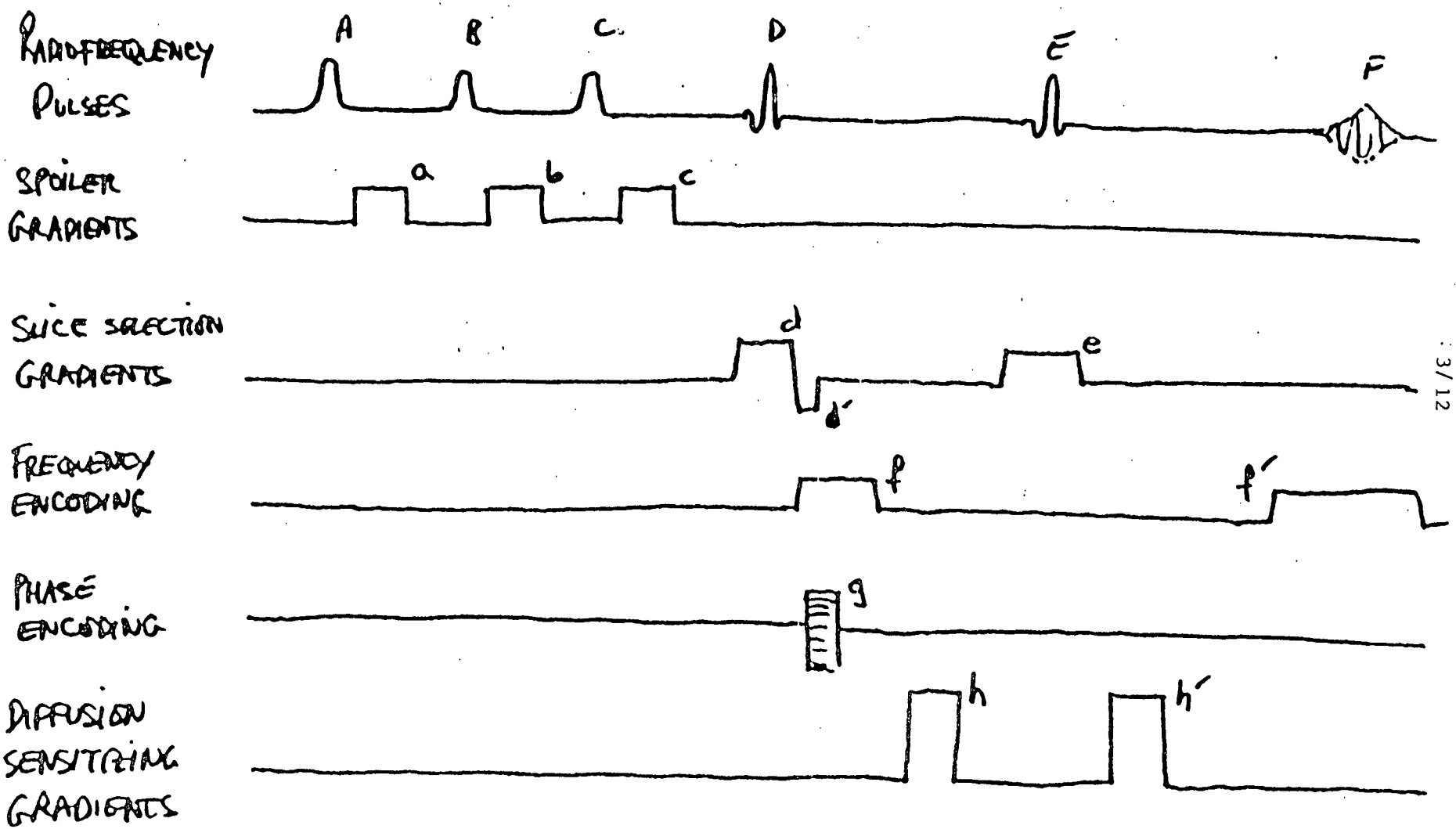
FIG 3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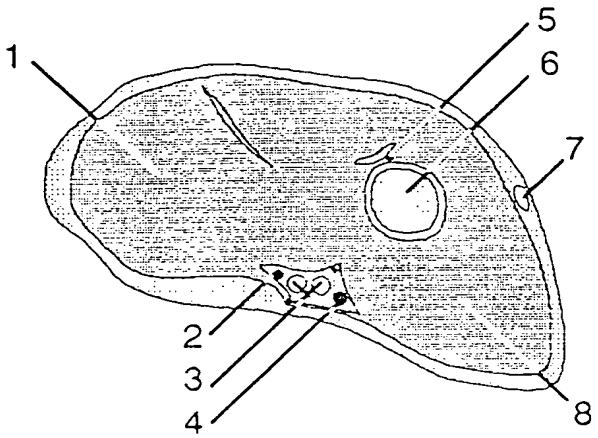

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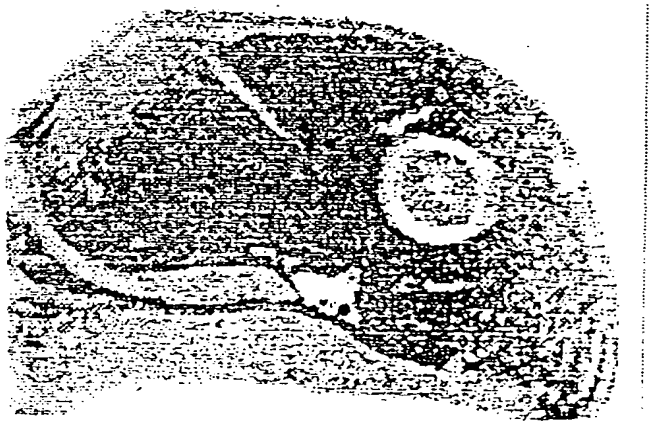

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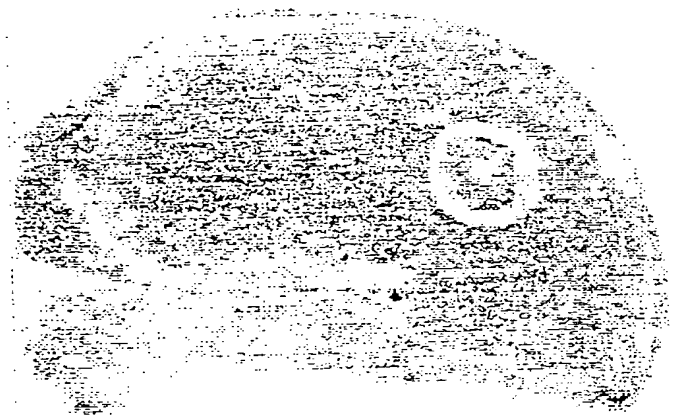

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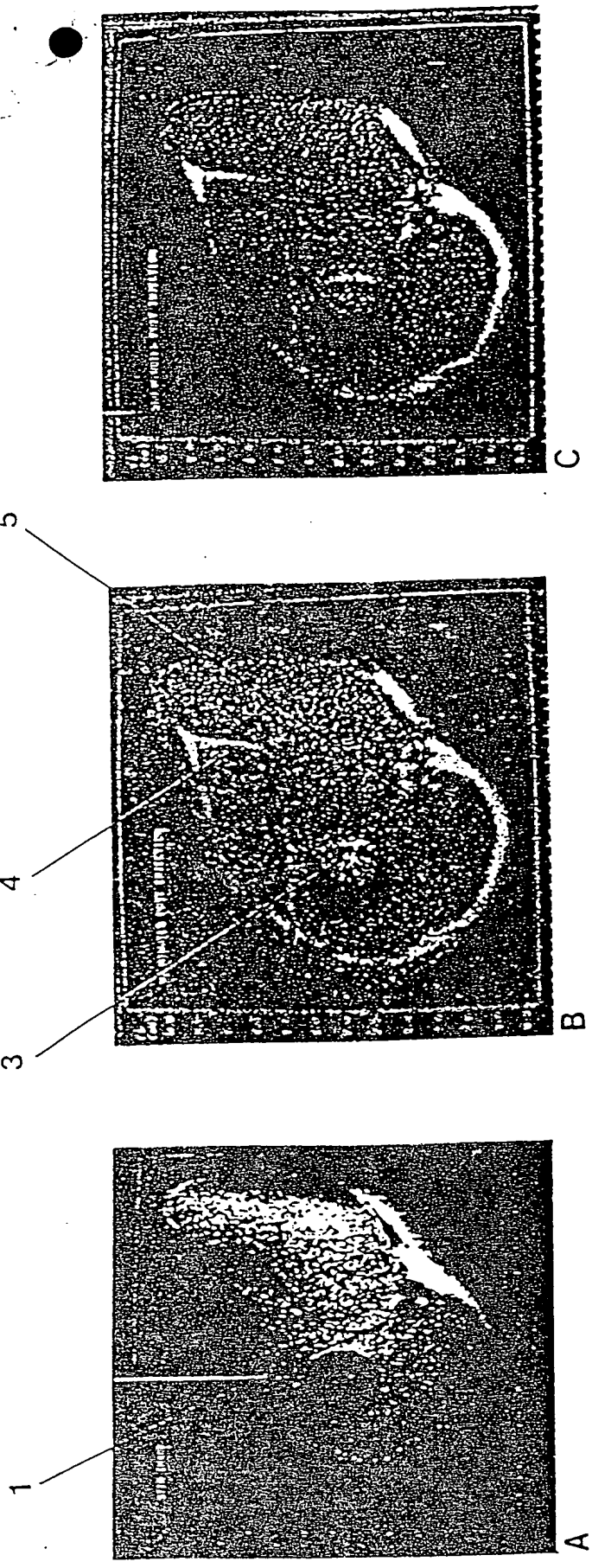

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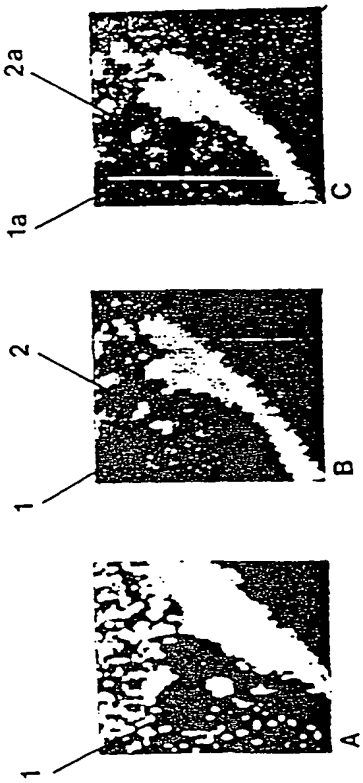

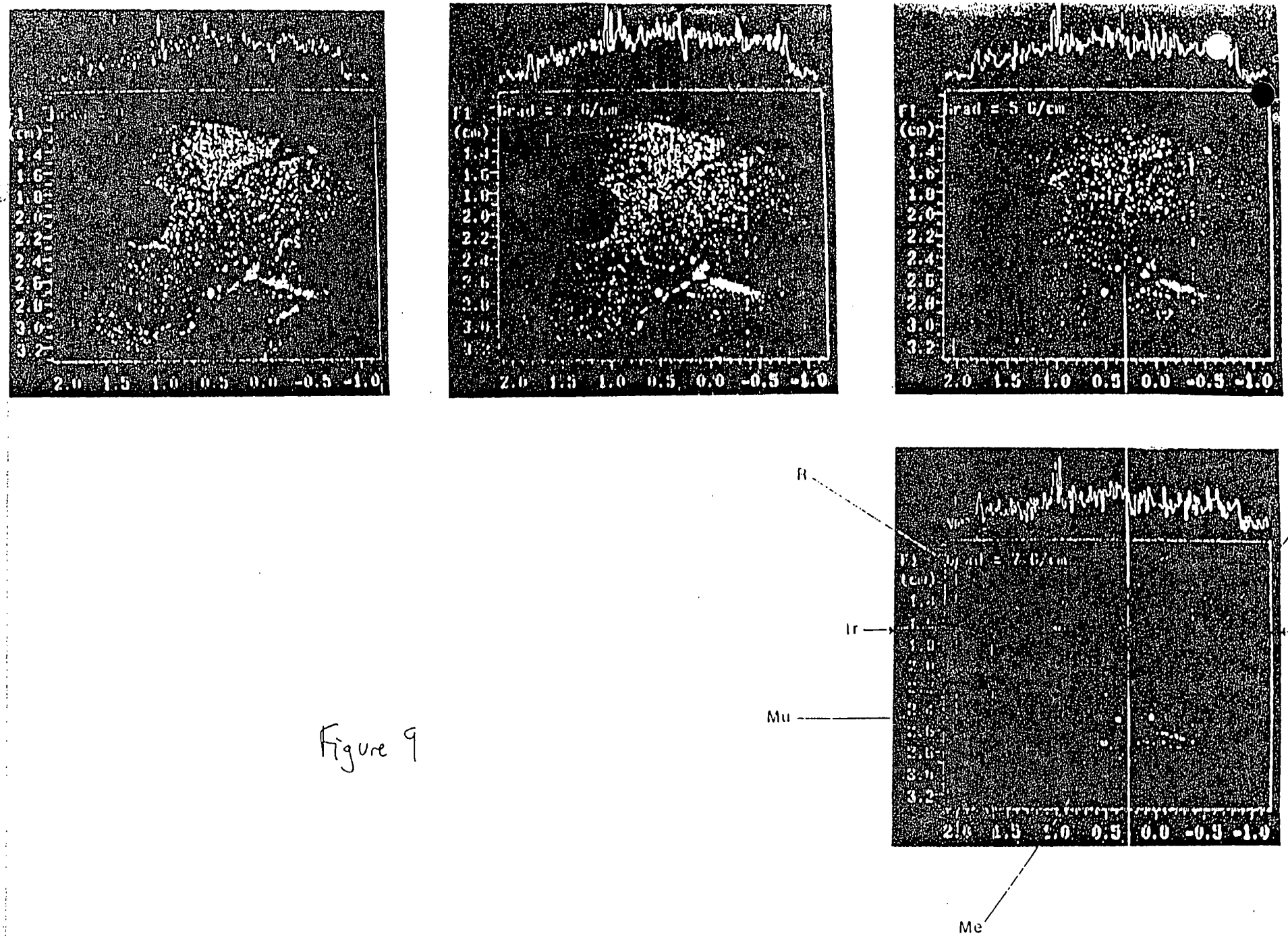

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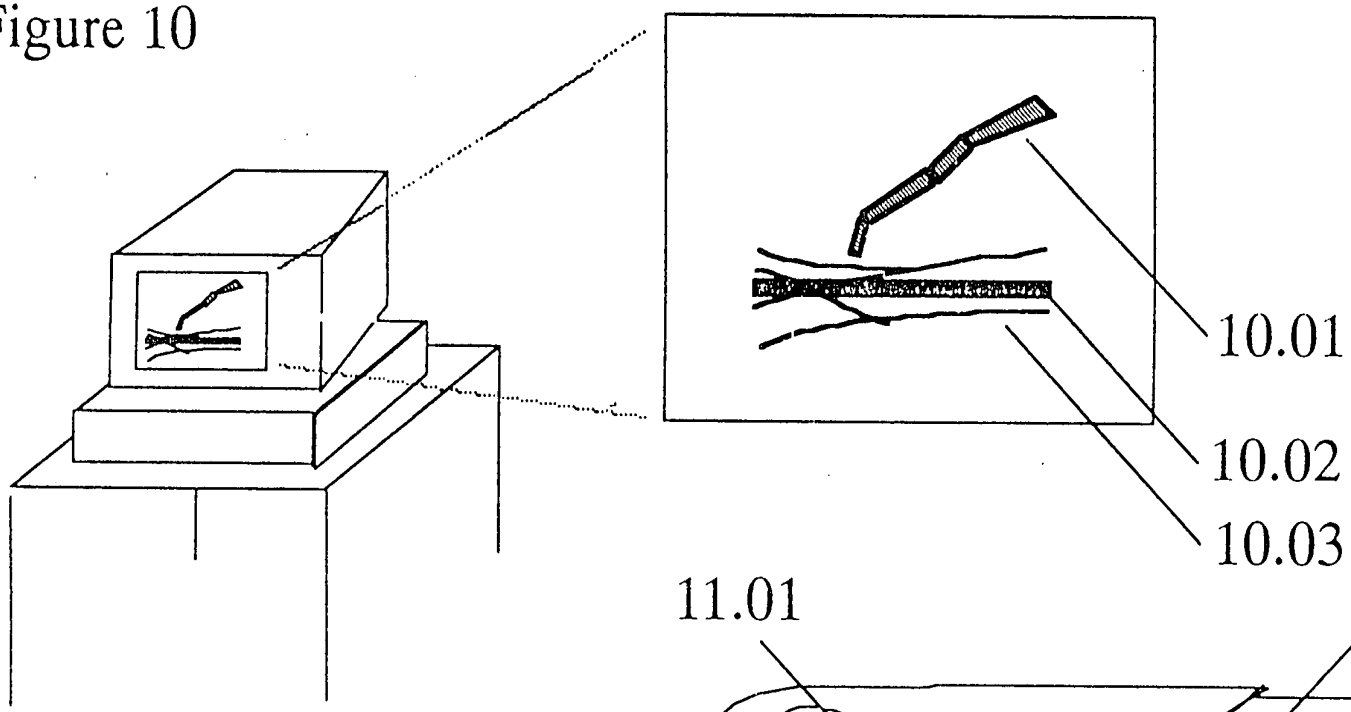

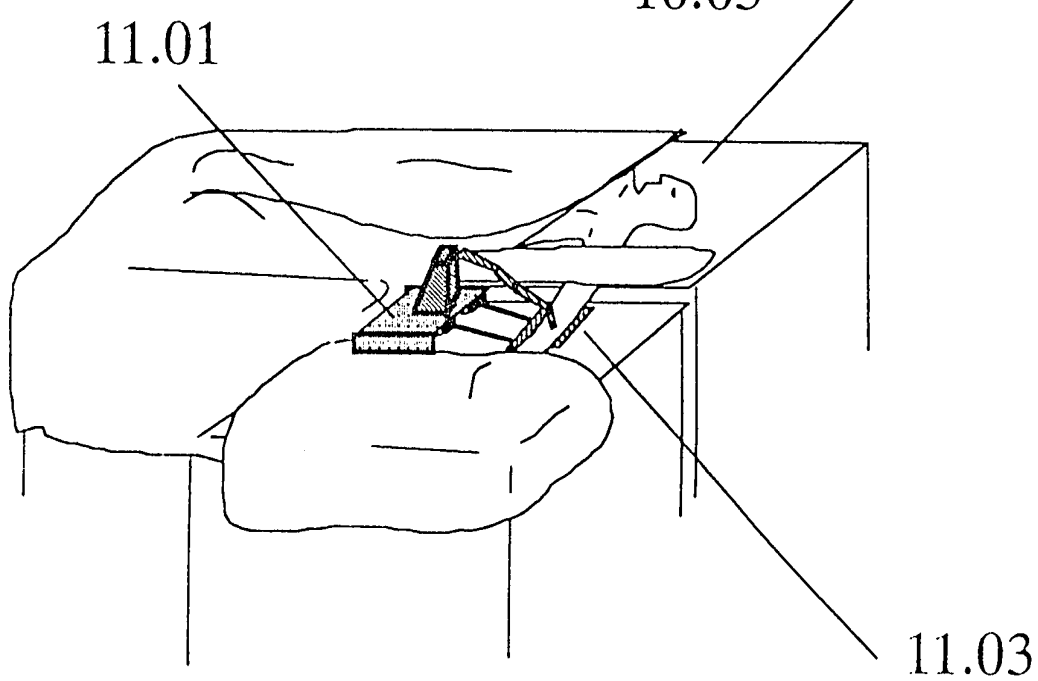

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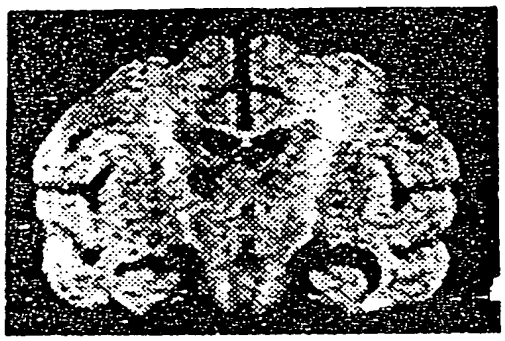

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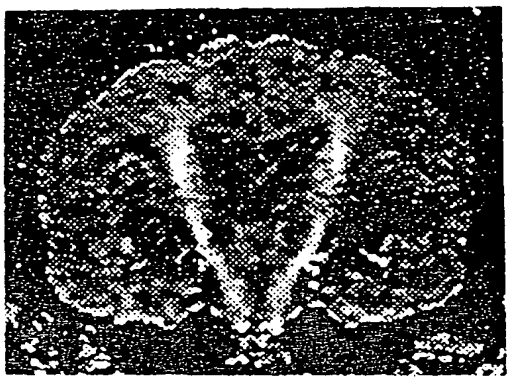

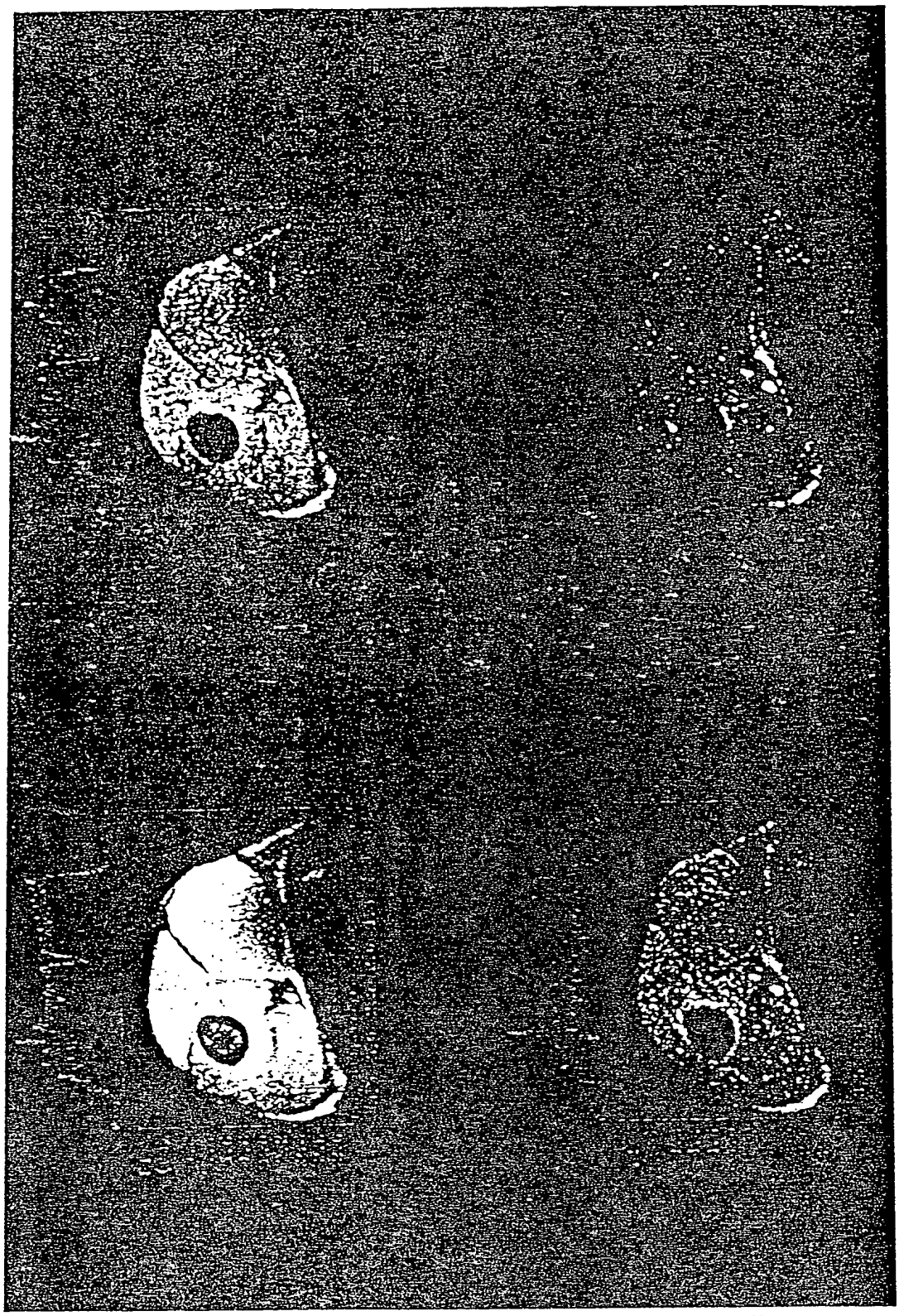

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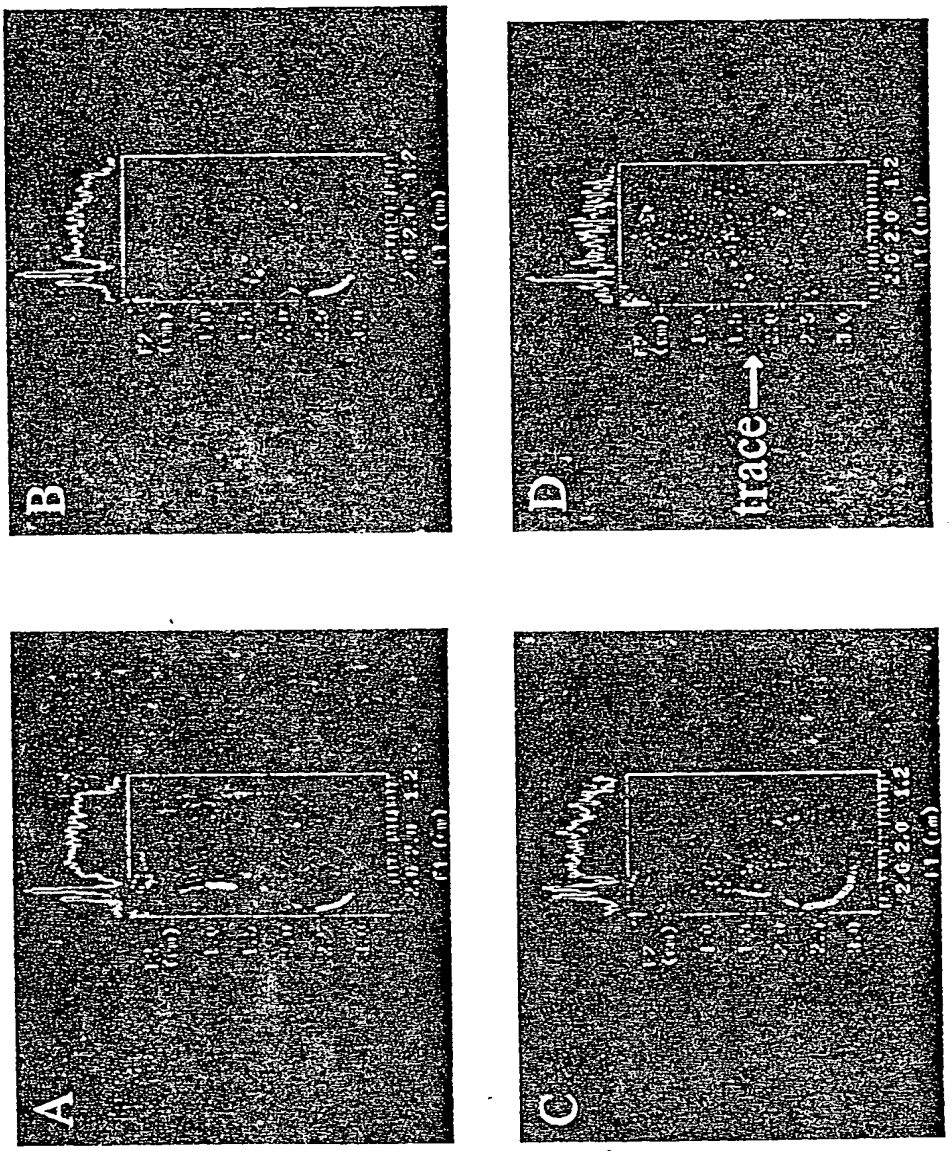

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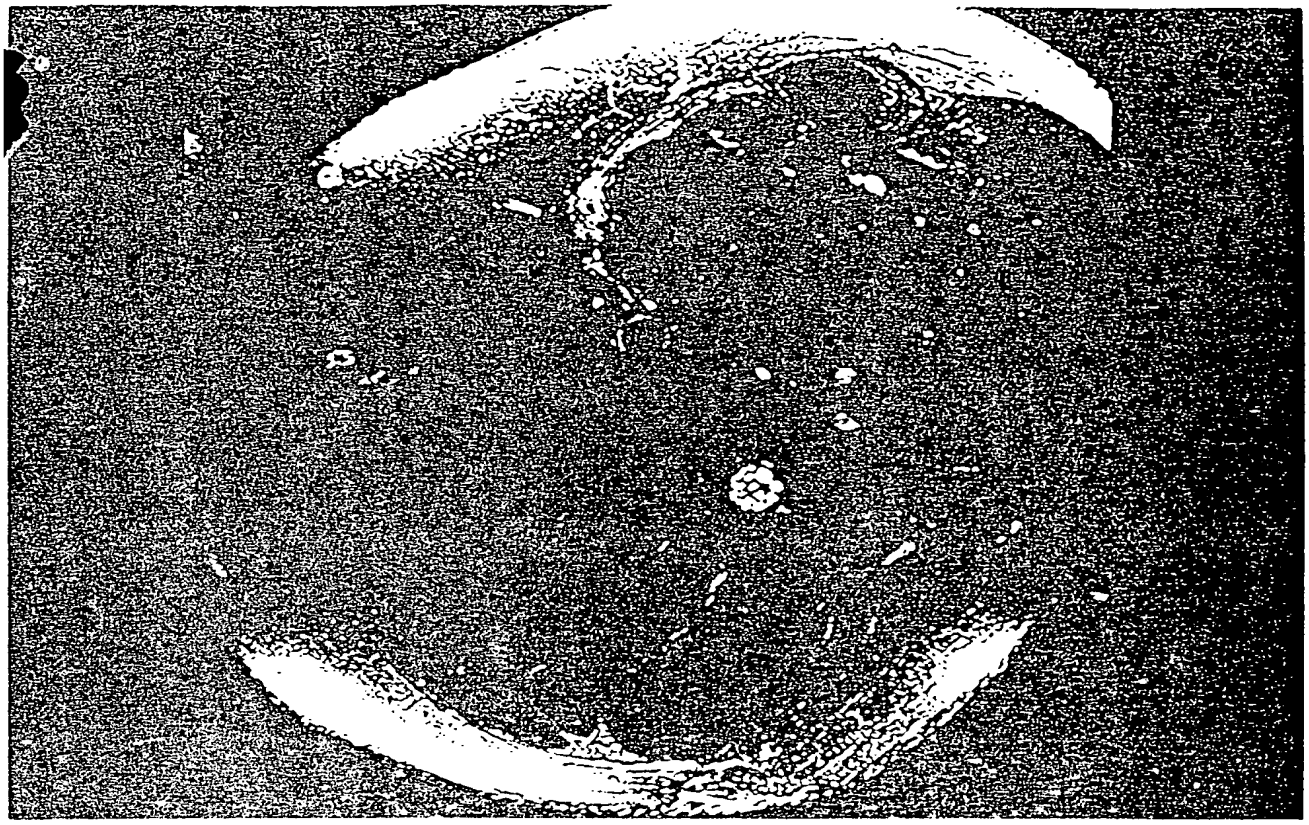

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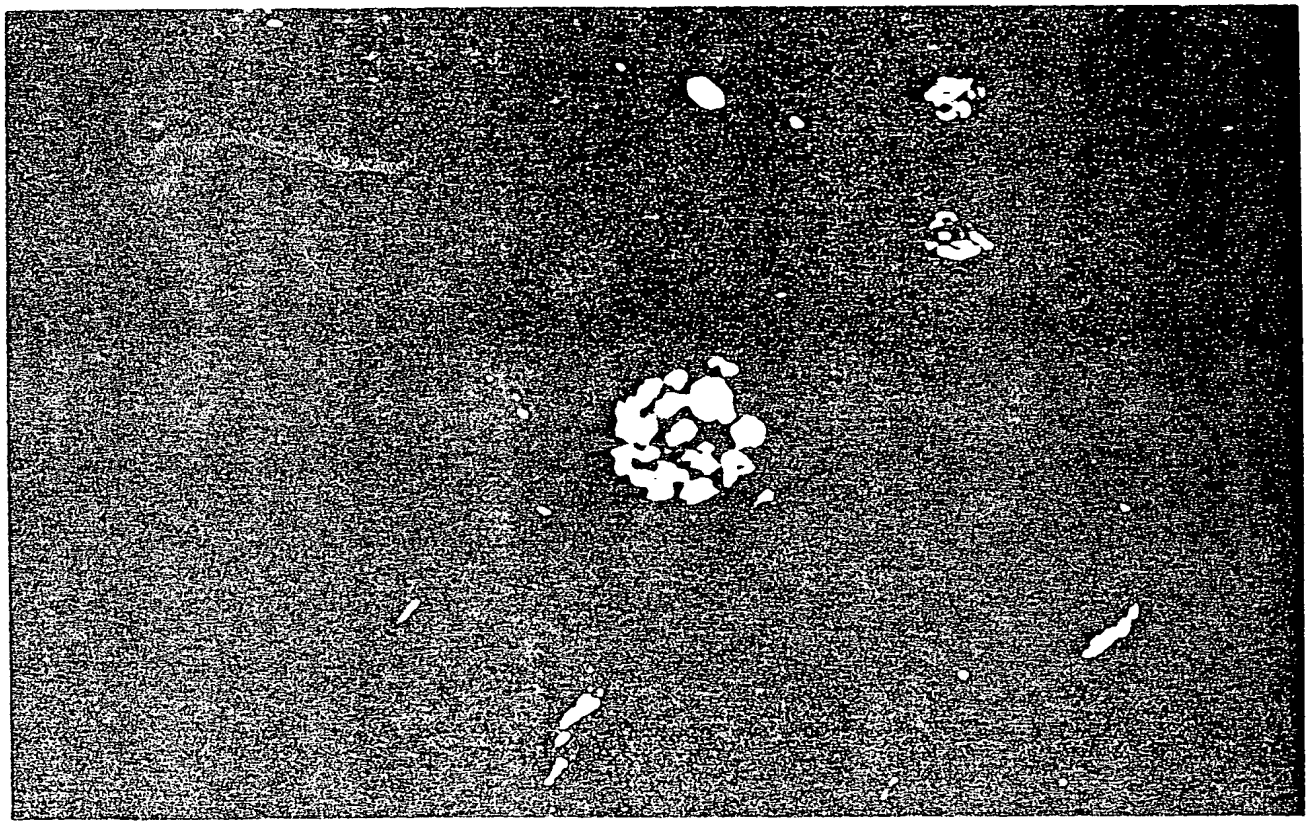

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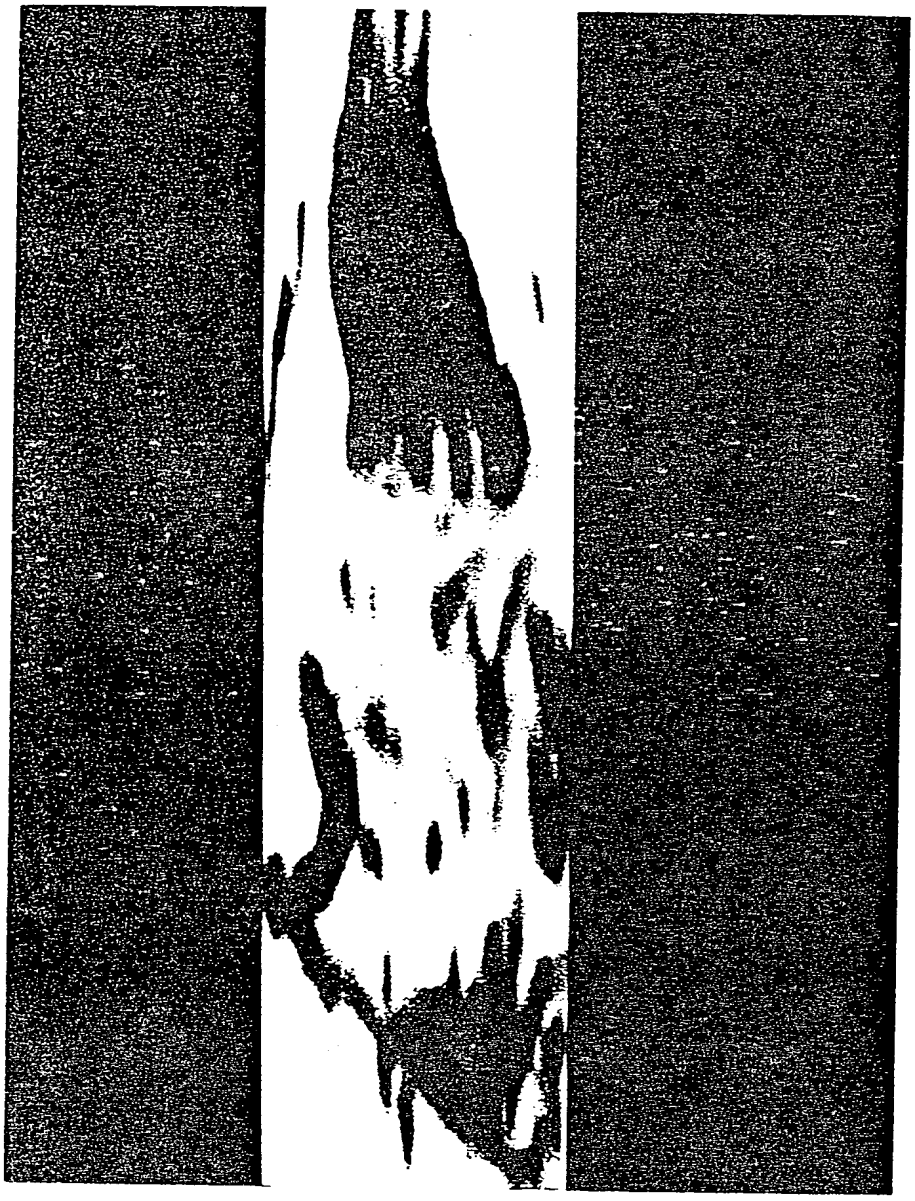

Figure 18

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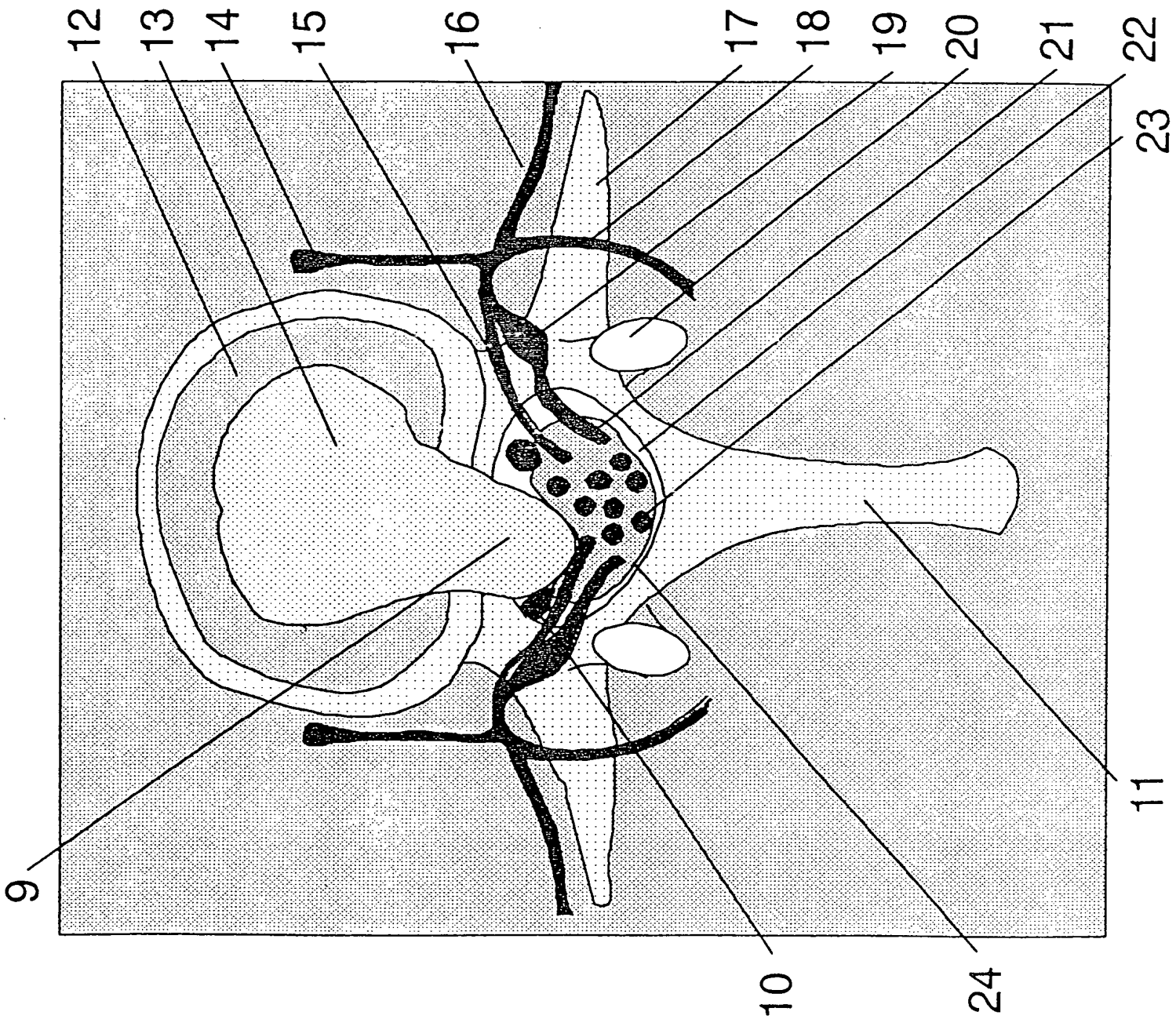

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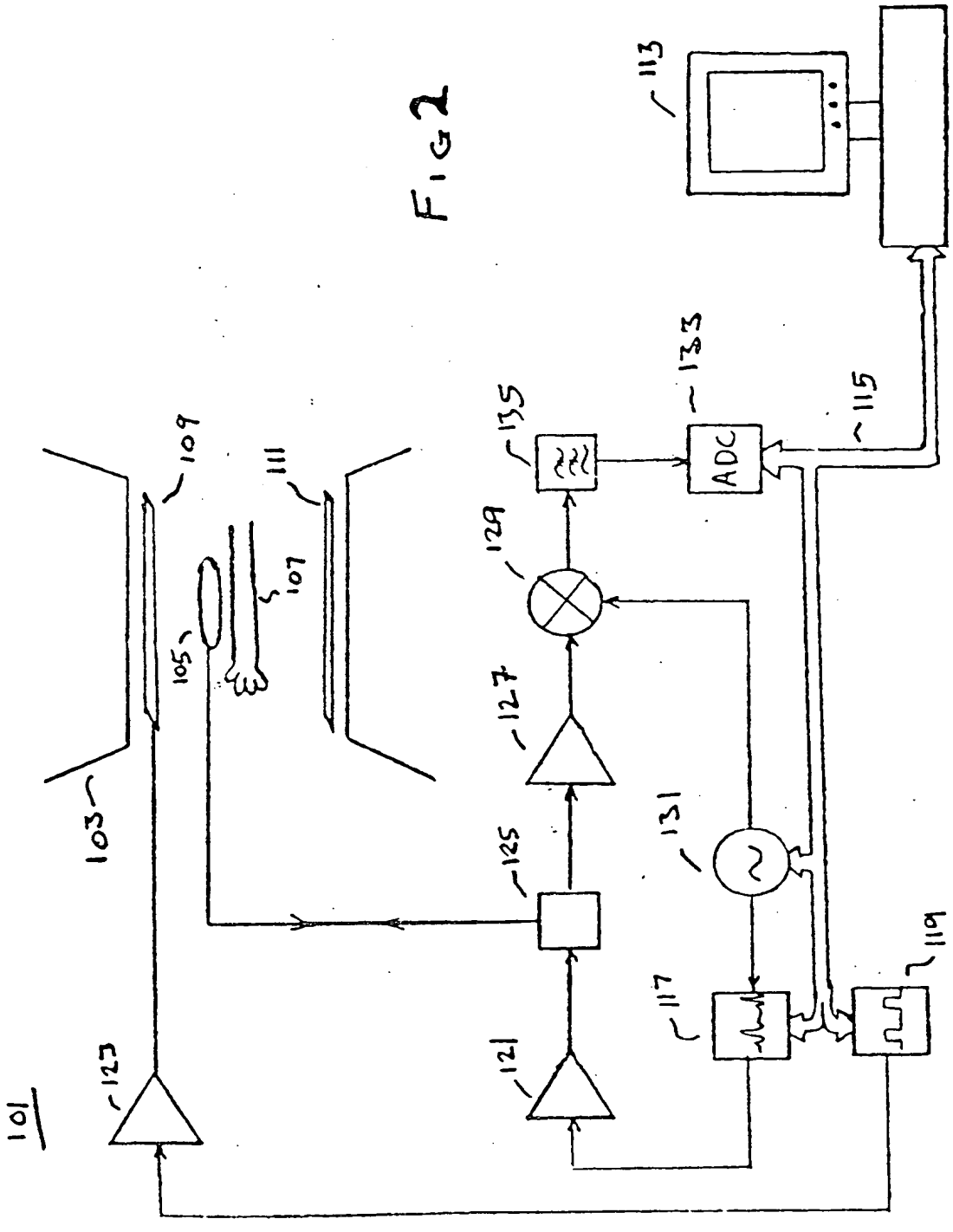
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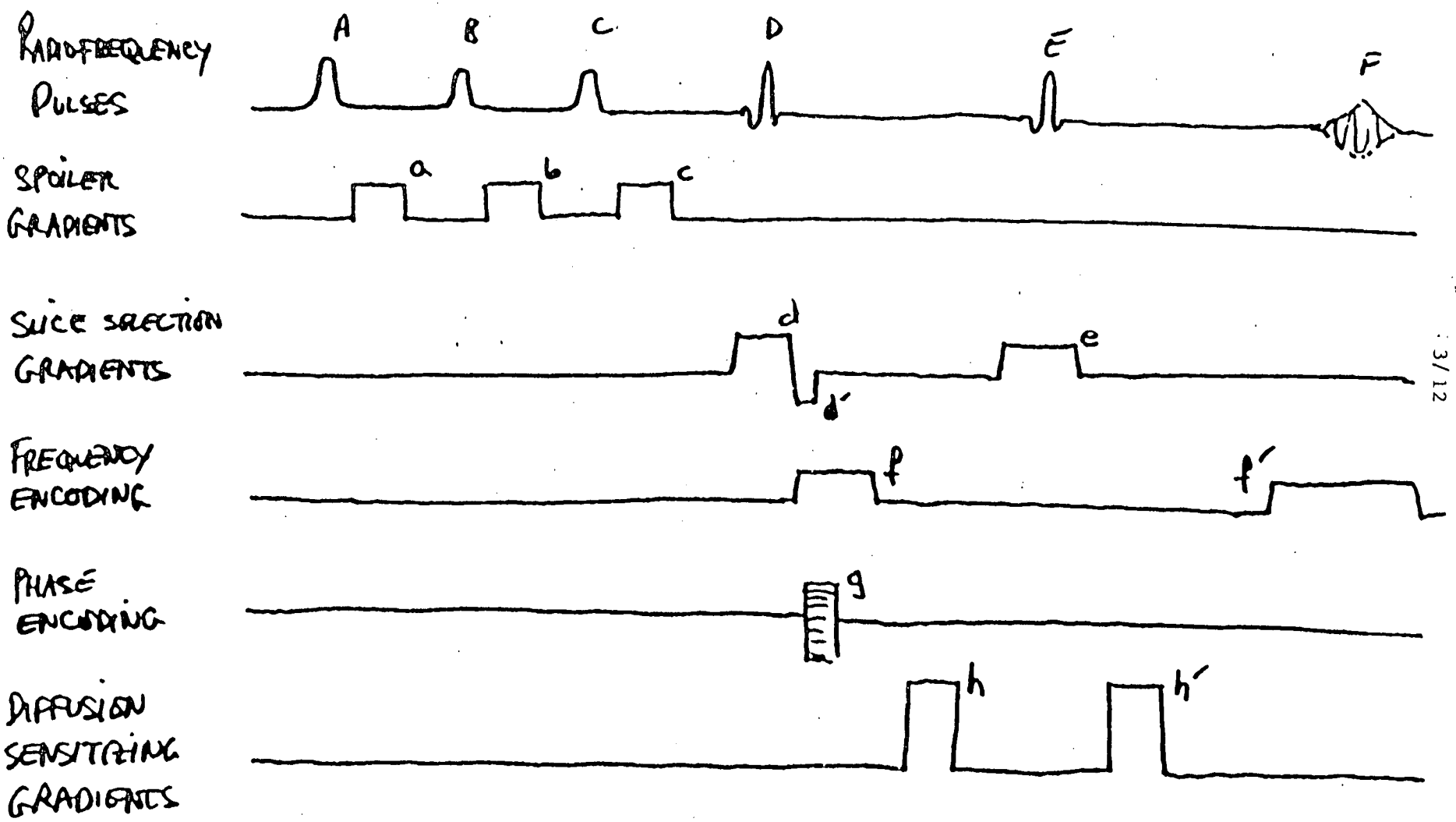
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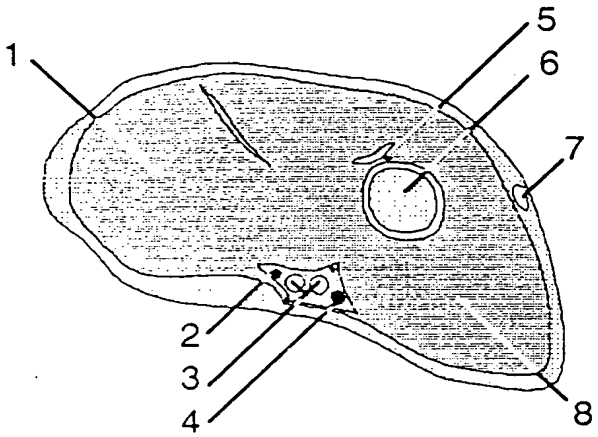

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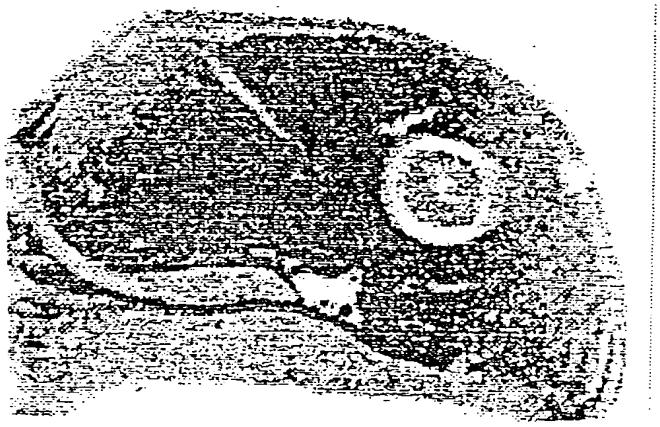

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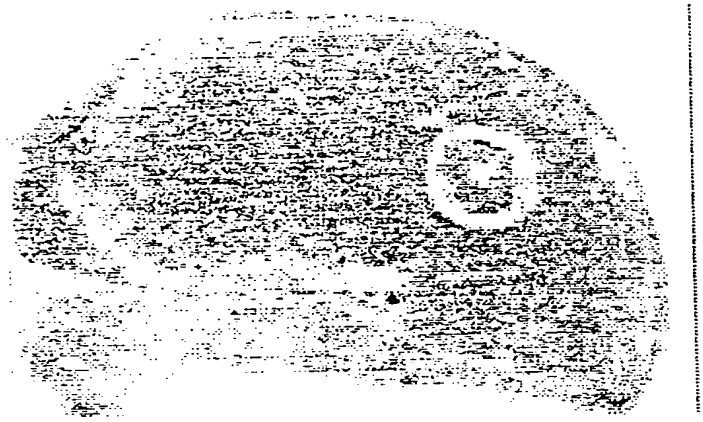

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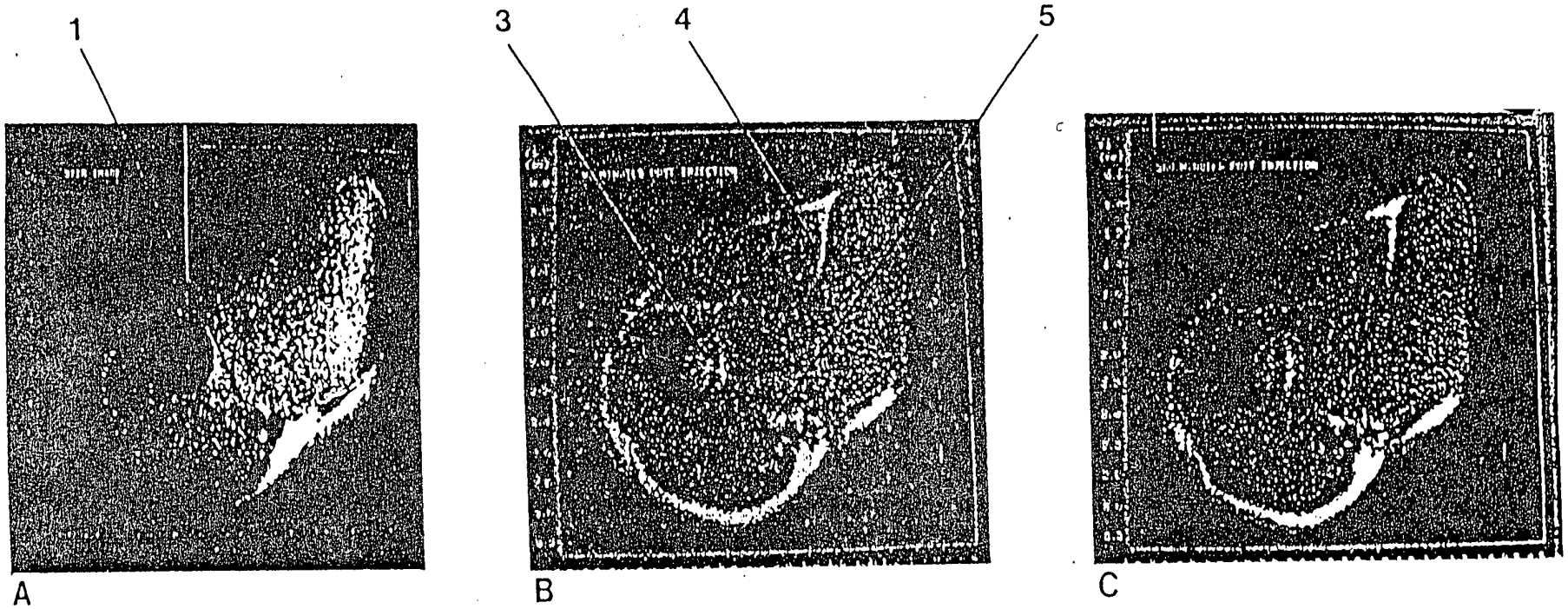

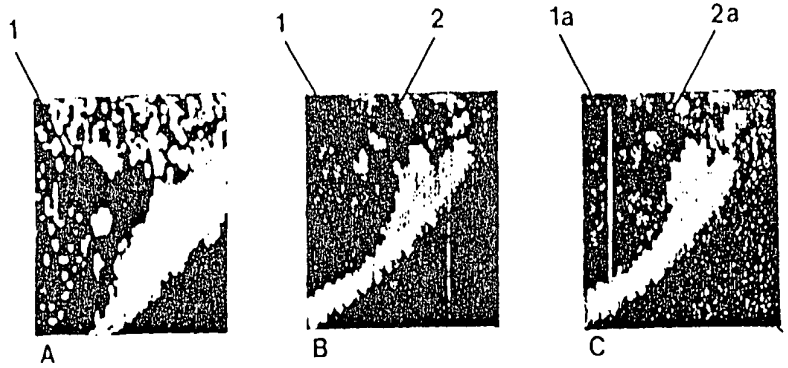

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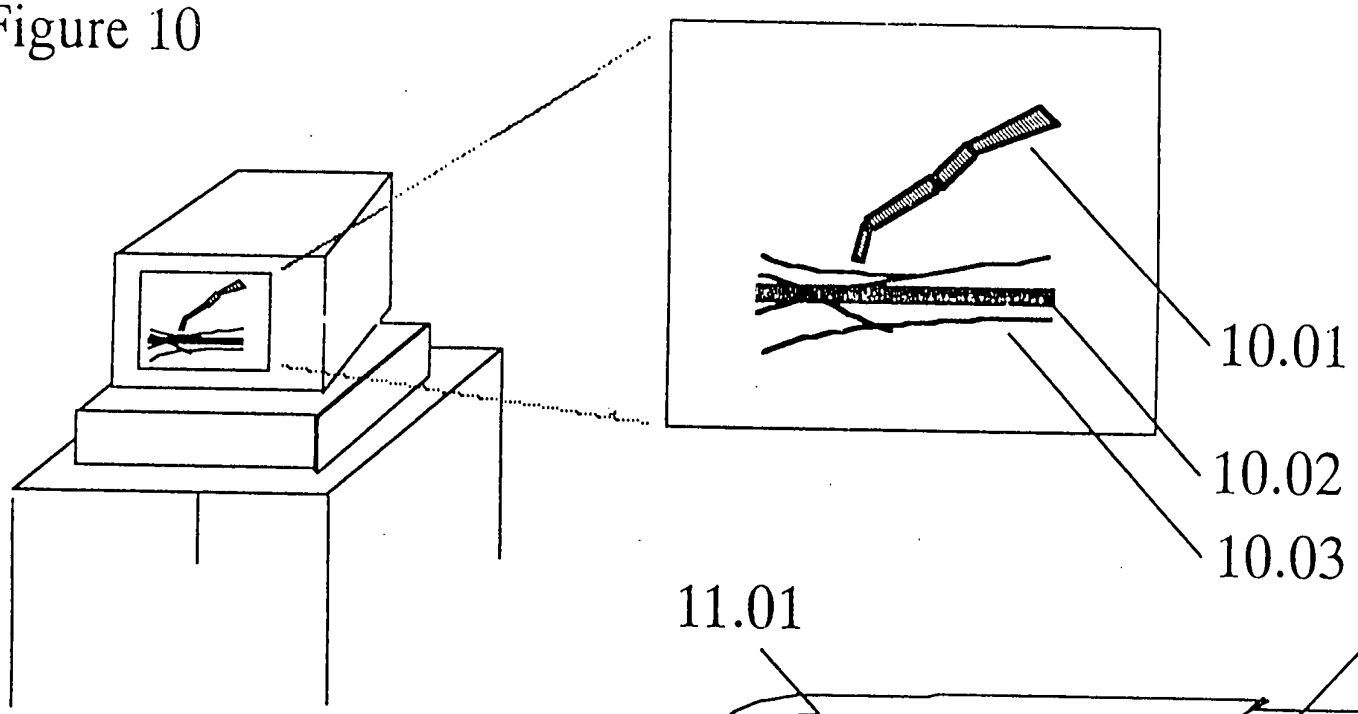

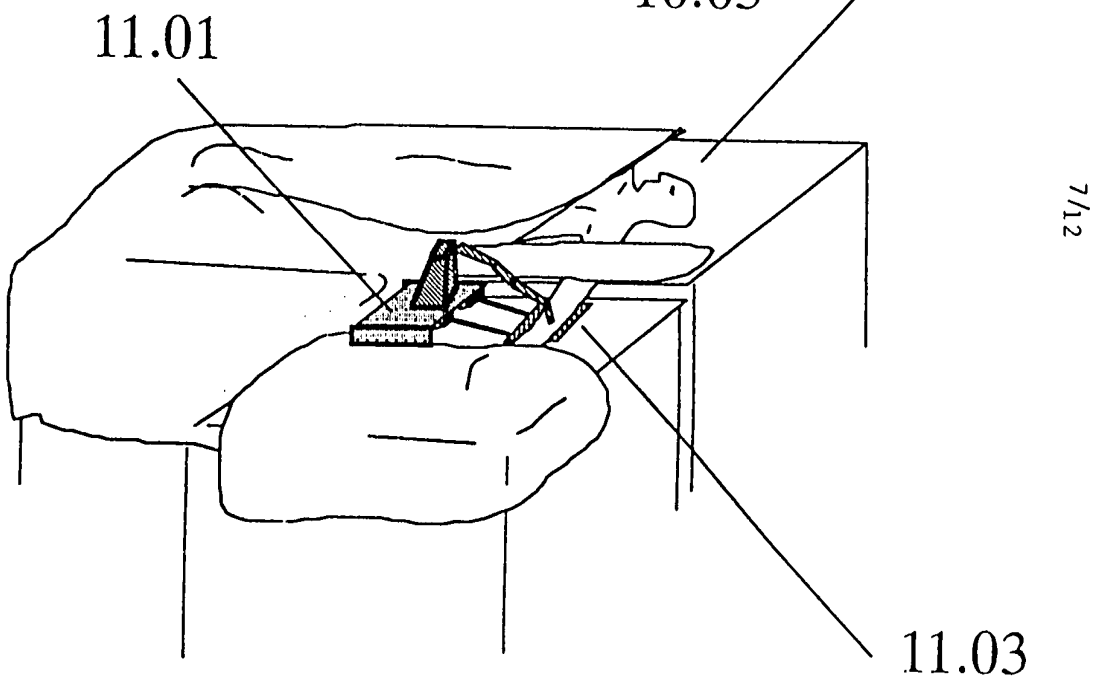

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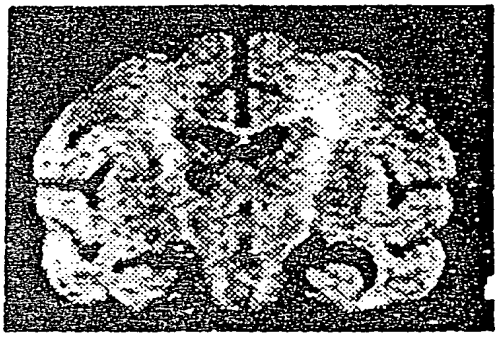

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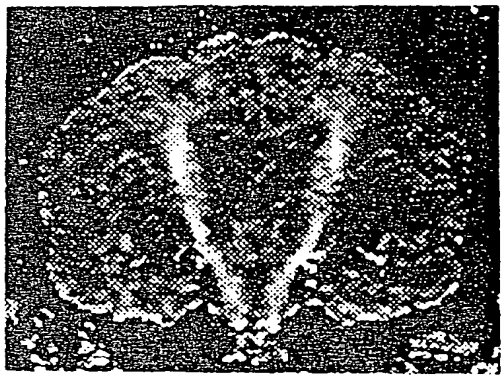

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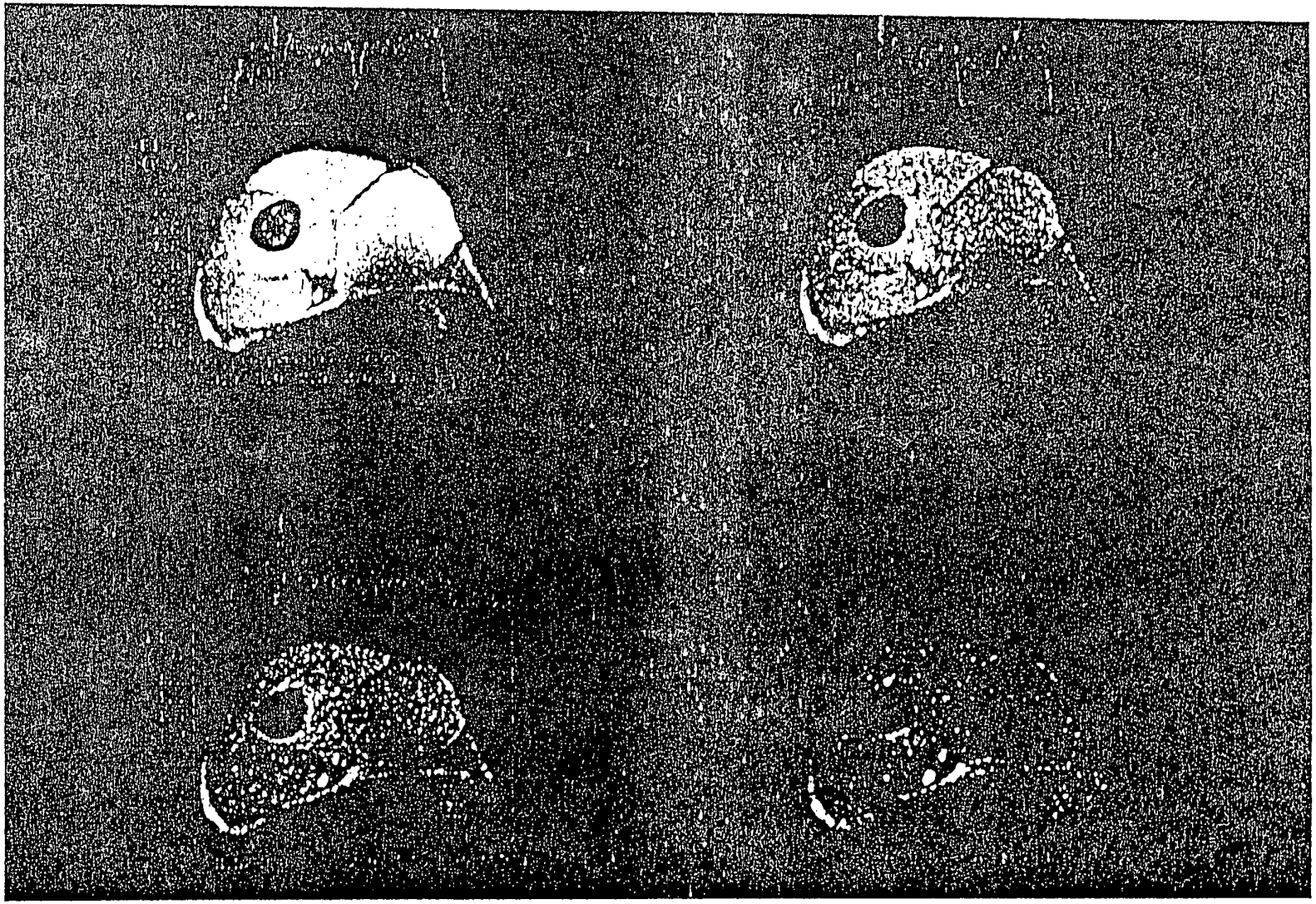

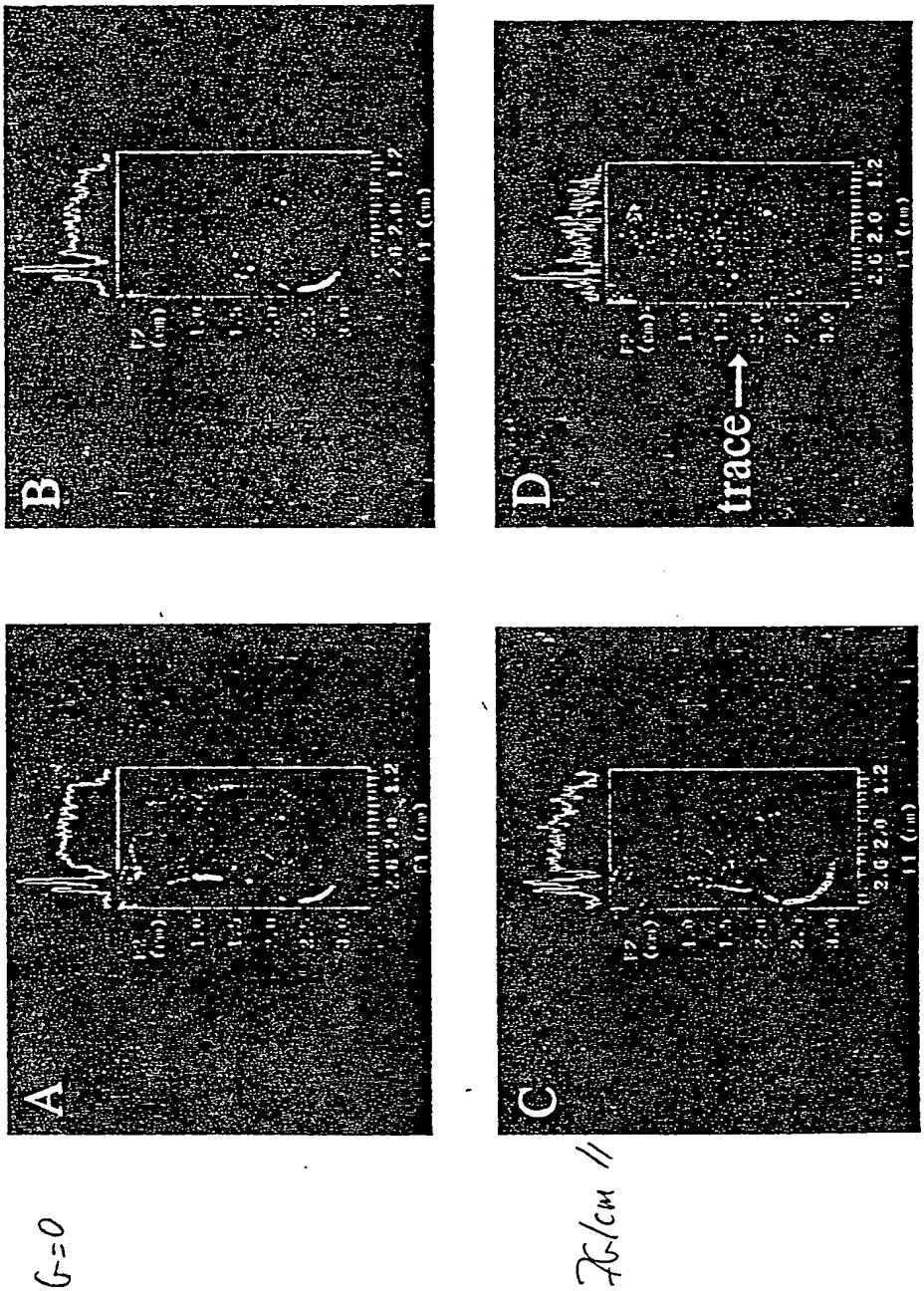

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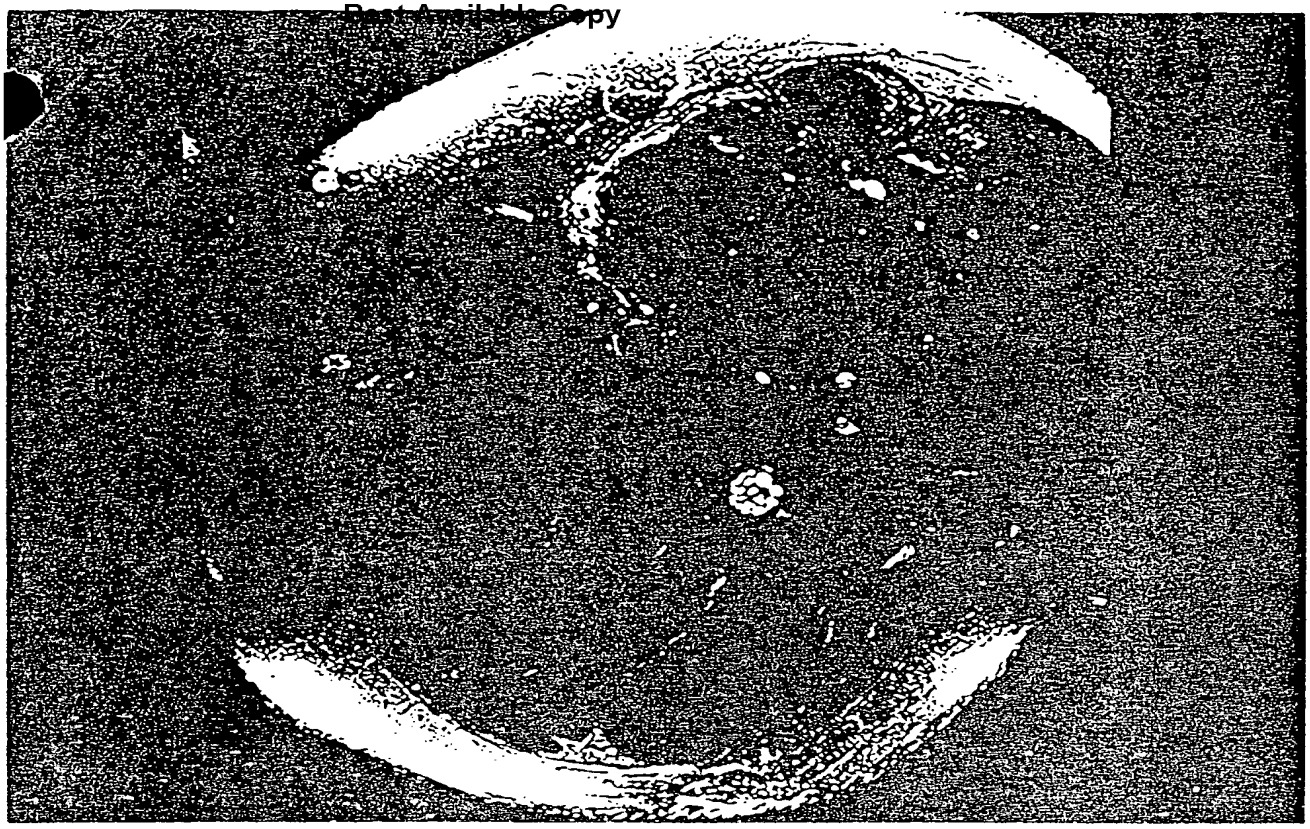

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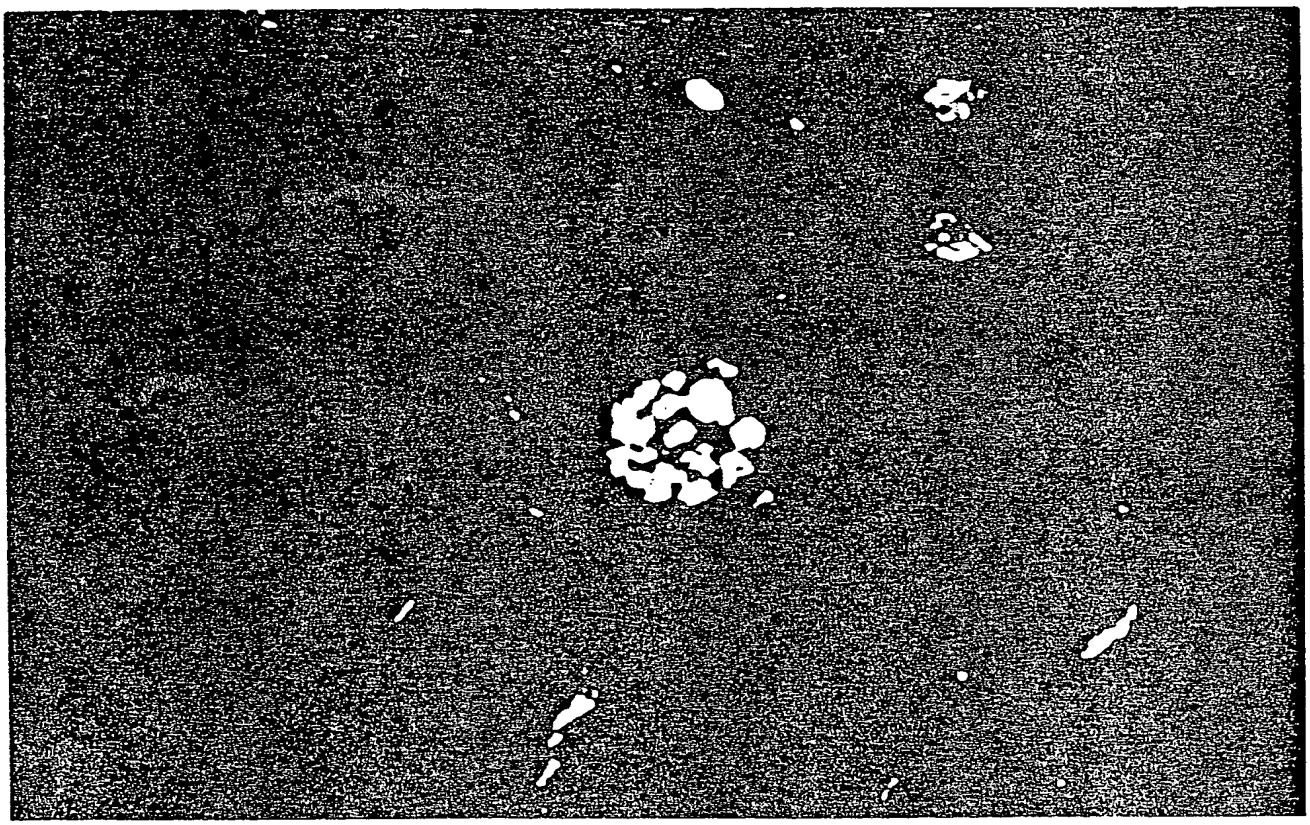

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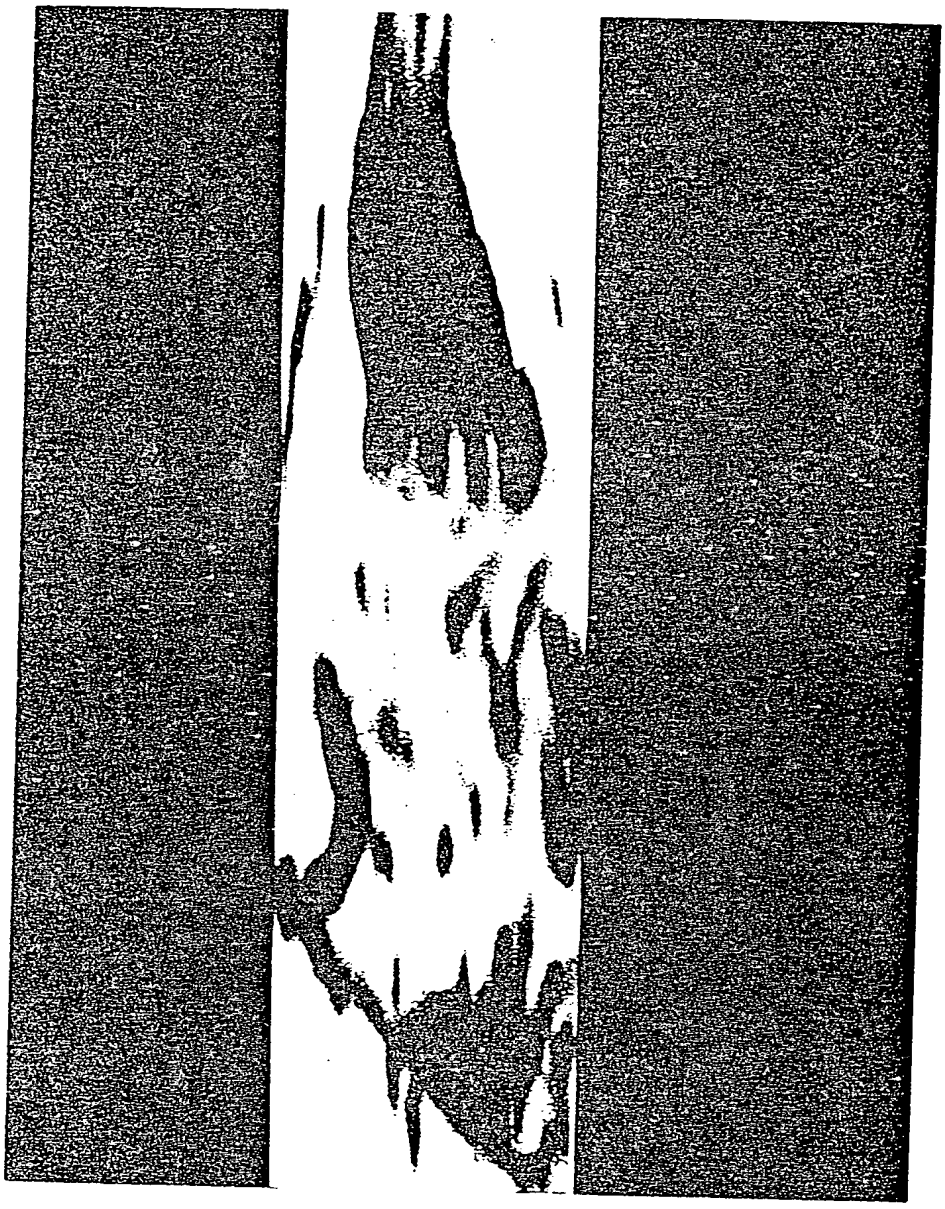

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